7.10 IBRUTINIB
Capsule 140 mg,
Imbruvica®, Janssen-Cilag Pty Ltd.

1 Purpose of Application

1.1 The minor resubmission requested Authority Required listings for two conditions:

- relapsed or refractory mantle cell lymphoma (MCL); and
- first-line treatment of patients with chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL) who are unsuitable for treatment with a fludarabine-based chemoimmunotherapy.

1.2 Ibrutinib was PBS listed on 1 December 2017 for the treatment of patients with relapsed or refractory CLL/SLL who are unsuitable for treatment with a purine analogue (i.e. fludarabine).

1.3 The minor resubmission proposed a [redacted] risk sharing arrangement (RSA) [redacted].

2 Background

2.1 Ibrutinib was previously considered by the PBAC:

- in November 2017 for first-line treatment of CLL/SLL; and
- in November 2017 and November 2016 for MCL.

2.2 The Public Summary Document (PSD) for this submission is presented in three parts:

(a) MCL;

(b) CLL/SLL; and

the [redacted].

<u>Relapsed/Refractory Mantle cell lymphoma</u>

3 Requested listing - MCL

3.1 The requested restriction for relapsed/refractory MCL was unchanged from the previous submission, and is presented below.

Name, restriction, manner of administration and form	Maximum Qty (units)	No. of Rpts	Dispensed price for maximum quantity	Proprietary name and manufacturer
Ibrutinib, 140 mg~~, oral~~, capsules~~,~~ *120*	~~120~~ *1*	5	Published: $[redacted] Effective (SPA): $[redacted] [a]	Imbruvica ® Janssen-Cilag Pty Ltd

Category/program:	GENERAL – General Schedule (Code GE)
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
PBS Indication:	Mantle cell lymphoma
Restriction level/method	☒Authority Required – Telephone
Initial treatment	
Clinical criteria	The condition must have relapsed or be refractory to at least one prior therapy AND Patient must have a WHO performance status of *0 or 1* ~~2 or less~~ AND The treatment must be the sole PBS-subsidised therapy for this condition *AND* *Patient must not have previously received PBS-subsidised treatment with this drug for this condition*
Administrative advice	Special Pricing Arrangements apply. *No increase in the maximum quantity or number of units may be authorised.* *No increase in the maximum number of repeats may be authorised.*
Continuing treatment phase	
Clinical criteria	The treatment must be the sole PBS-subsidised therapy for this condition AND Patient must have previously received PBS-subsidised treatment this drug for this condition AND ~~Patient must have stable or responding disease~~ *Patient must not develop disease progression while receiving PBS-subsidised treatment with this drug for this condition*
Administrative advice	Special Pricing Arrangements apply *No increase in the maximum quantity or number of units may be authorised.* *No increase in the maximum number of repeats may be authorised.*

[a] Per Table 1.18, p47 of the resubmission. This includes the Special Pricing Arrangement (published versus effective price). The economic model used a DPMQ of $[redacted] based on potential rebates from the proposed risk sharing arrangement.
Changes were made for consistency with the current PBS restriction for ibrutinib in relapsed/refractory SLL/CLL

3.2 The requested price (effective DPMQ of $[redacted]) was the same as per the previous submission, and the same as the requested price in first-line CLL/SLL. Consistent with first-line CLL, the resubmission assumed that the proposed RSA would reduce the cost to the Commonwealth (via a rebate) and applied a lower DMPQ in the economic model of $[redacted] (a [redacted]% reduction).

3.3 Per the previous submission, the proposed effective price per month for the MCL indication was the same as that proposed for first-line CLL/SLL. As the daily dose is higher in MCL (120 tablets a month for MCL versus 90 for CLL/SLL), the price per milligram was lower in MCL.

3.4 The re-submission proposed a criterion that the treatment must be the sole PBS subsidised therapy for this condition. The PBAC considered that the existing restriction for relapsed/refractory CLL/SLL should also have this criterion, and that this replace that "this treatment must be as monotherapy". This is on the basis of consistency with other oncology agents, consistency across ibrutinib indications and to ensure clarity guiding concurrent therapy.

3.5 The resubmission reiterated the previous request for a grandfathering clause, to enable patients receiving ibrutinib as part of a named patient program to access PBS-subsidised ibrutinib for continuing treatment. The previous submission stated that patients enrolled in the named patient program would meet the eligibility criteria of the proposed PBS restriction for continuing treatment. As the submission's estimates were based on an epidemiological approach and assumed a very high level of uptake, grandfathered patients were adequately accounted for in the budget impact analysis.

3.6 The pre-PBAC response stated that [redacted] patients with relapsed/refractory MCL had received ibrutinib under the named patient program between December 2014 and September 2017.

3.7 The PBAC considered that a grandfathering restriction would be appropriate for patients in the named patient program with stable or responding disease. The PBAC considered that the grandfather restriction should include the criteria:

> Patient must have previously received non-PBS-subsidised treatment with this drug for this condition prior to [listing date]
>
> AND
>
> Patient must have a WHO performance status score of 0 or 1
>
> AND
>
> The treatment must be the sole PBS-subsidised therapy for this condition
>
> AND
>
> Patient must not develop disease progression while receiving PBS-subsidised treatment with this drug for this condition.

For more detail on PBAC's view, see section 12 PBAC outcome.

4 Previous PBAC consideration - MCL

4.1 The outstanding matters of concern to the PBAC for the MCL indication are summarised in Table 1. In particular, the PBAC previously considered (in November 2017) that:

- the ICER/QALY resulting from Scenario 4 of the model, $105,000/QALY - $200,000/QALY gained, was unacceptably high particularly in the context of the uncertain incremental benefit of ibrutinib compared with R-CHOP; and
- patient numbers were significantly overestimated; lower estimates would be required for an RSA to be useful (PSD, ibrutinib MCL, November 2017, Paragraphs 7.7 to 7.9).

Table 1: Summary of outstanding matters of concern – MCL

Component	Matter of concern (November 2017 Minutes)	How the resubmission addressed it
Economic model		
DPMQ	$[redacted] per month (for 1 x 120 capsule bottle)	Unchanged. $[redacted] was used in the model ([redacted]% lower) based on potential RSA rebate, assuming utilisation would be at the estimated level.
ICER	ICER for Scenario 4: $[redacted] PBAC considered the ICER was unacceptably high particularly in the context of the uncertain incremental benefit vs R-CHOP [Para 7.6, 7.7].	ICER for Scenario 4: $[redacted] Only change was cost of ibrutinib due to application of the RSA.
Financial estimates		
Patient numbers	[redacted] pts over 5 years [Para 7.8] PBAC considered patient numbers were significantly overestimated as: -uptake rate ([redacted]%) overestimated, especially use of same uptake in prevalent and incident patients; -potential for leakage outside intended population; -% who relapse and receive 2nd-line treatment ([redacted]%) and % with WHO scores ≤2 ([redacted]%) were uncertain.	[redacted] pts over 5 years Patient numbers reduced because uptake rate was reduced from [redacted]% to [redacted]% (consistent with 1st-line and r/r CLL/SLL). Same rate was used in prevalent and incident pts.
PBS/RPBS cost over 5 yrs without offsets	Without RSA: $60 - $100 million over 5 years	Without RSA: $60 - $100 million With RSA: $60 - $100 million ([redacted]% reduction vs without RSA)
PBS/RPBS cost over 5 yrs with offsets	Without RSA: $60 - $100 million over 5 years	Without RSA: $60 - $100 million With RSA: $30 - $60 million
RSA	[Para 7.9] PBAC considered that patient numbers would need to be revised to lower estimates for an RSA to be useful	RSA proposed [redacted].

Source: November 2017 PBAC minutes and the resubmission

CLL = chronic lymphocytic leukaemia; DPMQ = dispensed price for maximum quantity; ICER = incremental cost-effectiveness ratio; PBAC = Pharmaceutical Benefits Advisory Committee; PBS = Pharmaceutical Benefits Scheme; pts = patients; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone; RSA = risk sharing arrangement; SLL = small lymphocytic lymphoma; yrs = years

5 Comparator - MCL

For MCL, the comparator was unchanged from the previous submission, which was rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP). This was previously accepted by the PBAC.

6 Consideration of the evidence - MCL

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) and organisations (1) via the Consumer Comments facility on the PBS website, which related to the use of ibrutinib in CLL/SLL (refer to Section 10).

Clinical claim

6.3 For MCL, the resubmission claimed that ibrutinib had superior efficacy versus R-CHOP and superior comparative safety versus active treatment with R-CHOP. The PBAC previously accepted these claims (PSD, ibrutinib (MCL), November 2017 Paragraphs 7.3 and 7.4).

Economic analysis

6.4 For MCL, the resubmission stated that the only changes to the economic model were that the cost of ibrutinib was reduced to reflect the potential impact of the proposed RSA and dispensing fees and mark-ups were updated (to reflect fees at 1 December 2017). As a minor submission, these changes were not evaluated.

6.5 The resubmission presented the same four scenarios from the previous submission, which explored the impact of treatment crossover and converging of the overall survival curves at 10 years. In its previous consideration (November 2017), the PBAC had expressed a preference for Scenario 4 (convergence at ten years, no adjustment for crossover in the pivotal trial). The PBAC (November 2017) had considered that Scenario 4 "still reflected optimistic assumptions given the uncertain magnitude of the incremental benefit, convergence to ten years and the utility differences between the treatment arms" (PSD, ibrutinib MCL, November 2017, Paragraph 7.6).

6.6 The pre-PBAC response stated that a scenario-based ICER range would provide a more appropriate estimation of the cost-effectiveness of ibrutinib in MCL, rather than basing the ICER on a single, more conservative scenario. The PBAC noted that no additional evidence was provided to support a change to its previous consideration.

6.7 The results of the economic evaluation for Scenario 4 are presented in the table below.

Table 2: Incremental health outcomes obtained in the economic evaluation (discounted) based on resubmission [a]

Costs			Health outcomes			ICER
Ibrutinib	R-CHOP	Increment	Ibrutinib	R-CHOP	Increment	
Current resubmission: Scenario 4 [b] OS convergence at ten years; ITT population (rather than crossover-adjusted)						
$[redacted]	$[redacted]	$[redacted]	[redacted] QALY	[redacted] QALY	[redacted] QALY	**$[redacted]/QALY** [c]
Current submission: without RSA rebate applied to price of ibrutinib (i.e. DPMQ of $[redacted] applied)						
$[redacted]	$[redacted]	$[redacted]	[redacted] QALY	[redacted] QALY	[redacted] QALY	$[redacted]/QALY
November 2017 submission: Scenario 4						
$[redacted]	$[redacted]	$[redacted]	2.08 QALY	1.55 QALY	0.53 QALY	$[redacted]/QALY

Source: Tables 1.22 and 1.23, p 51-52 of the resubmission; Table 13, p22 of the ibrutinib (MCL) PBAC Minutes, November 2017.
ICER = incremental cost-effectiveness ratio; OS = overall survival; ITT = intention to treat; QALY = quality-adjusted life year; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; ital = figures in italics were corrected during evaluation
[a] In the resubmission, the AEMP was calculated by: [redacted]. [b] Only the ICER for Scenario 4 is presented. In the PBAC's previous consideration, the PBAC noted that the submission had presented scenario analyses to generate four ICERs. The PBAC considered that Scenarios 1 and 3 were overly optimistic as the overall survival curves did not converge within the model time horizon. Scenario 2 was considered uncertain, and likely optimistic, given it (along with Scenario 1) was based on adjusted trial results… Overall, the PBAC considered that Scenario 4 had addressed many of its previous concerns. (Paragraphs 7.5 and 7.6, ibrutinib (MCL) PBAC Minutes, November 2017)
[c] The pre-PBAC response stated that the ICER was revised to $[redacted]/QALY due to the "changes to the overall financial estimates". The basis for this change was unclear.

6.8 The ICER for Scenario 4 reduced from $105,000/QALY-$200,000/QALY in the previous submission to $45,000/QALY-$75,000/QALY in the resubmission due to the assumption that [redacted]% of Commonwealth expenditure on ibrutinib would be rebated through the RSA. This assumed that utilisation would be at the levels estimated by the resubmission. If utilisation was lower ([redacted]), then the ICER would be higher. The resubmission did not test this in sensitivity analyses.

Estimated PBS usage & financial implications

6.9 In its November 2017 consideration of ibrutinib for MCL, the PBAC had "considered that the patient numbers were significantly overestimated" and highlighted that "the uptake rate ([redacted]%) was overestimated" (PSD, November 2017,Paragraph 7.8). The PBAC considered that this was "in part due to assuming … the same uptake for prevalent and incident patients" (PSD, November 2017, Paragraph 6.85). Further, the PBAC considered that there was potential for leakage of ibrutinib outside the intended patient population, for example as use in the first-line setting in patients unable to tolerate R-CHOP (Paragraph 6.85). The PBAC had considered that patient numbers would need to be revised to lower estimates for a RSA to be useful (PSD, ibrutinib (MCL), November 2017 Paragraph 7.9).

6.10 To address this, the resubmission reduced the uptake rate from [redacted]% to [redacted]% in both prevalent and incident patients. This was based on the uptake rate that had previously been used for ibrutinib in relapsed/refractory CLL/SLL.

6.11 The pre-PBAC response stated that the uptake rate ([redacted]%) was appropriate because the financial estimates had already removed patients with a WHO performance status > 2, which accounted for patients who would not be fit to receive active therapy. Further, the pre-PBAC response justified the use of the same uptake rate in prevalent and incident patients because the two groups were assumed to have differing proportions of patients with WHO performance status of ≤ 2. That is, [redacted]% of prevalent patients and [redacted]% of incident patients were assumed to have a WHO performance status of ≤ 2.

6.12 The revised financial estimates are shown in Table 3.

Table 3: Estimated use and financial implications of ibrutinib listing in relapsed/refractory MCL – without the RSA

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of ibrutinib use						
Patients initiating treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of packs dispensed [a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Previous submission (November 2017)						
Patients initiating treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of scripts dispensed [a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated financial implications of ibrutinib without offsets (basis of RSA)						
Cost to PBS/RPBS less copayments	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Estimated financial implications for R-CHOP and pegfilgrastim						
Cost to PBS/RPBS for substituted drugs	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
Estimated net cost to PBS/RPBS/MBS – without the RSA						
Net cost to PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net cost to MBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net cost to PBS/RPBS + MBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Previous submission (November 2017) [b]						
Cost to PBS/RPBS less copayments	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Cost to PBS/RPB for substituted drugs	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
Net cost to PBS/RPBS (with offsets)	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net cost to PBS/RPBS + MBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]

Source: Tables 1.11 to 1.12, pp36-38 of the minor resubmission.
MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; RPBS = Repatriation Pharmaceutical Benefits Scheme
[a] Average of [redacted] months treatment per patient, based on the Kaplan-Meier estimates for progression free survival from the economic model (treatment months x [redacted]% (dose intensity)).
[b] As reported in the resubmission (using 1 December 2017 dispensing fees and mark-ups).

6.13 At Year 5, the estimated number of patients initiating treatment was [redacted] and the estimated net cost to the PBS/RPBS would be $10 -$20 million without the RSA.

6.14 The estimated cost to the PBS/RPBS (without offsets) reduced from $60 -$100 million over five years (previous submission) to $60 -$100 million over five years without the proposed RSA, or a maximum cost to the PBS/RPBS of $60 -$100 million over five years with the RSA (refer to Section 11).

6.15 The reduced uptake rate led to a corresponding [redacted]% reduction in patient numbers (from [redacted] to [redacted] over five years).

6.16 The resubmission did not address the following issues raised in the PBAC's previous consideration:

- the treatment duration ([redacted] months), which was based on the economic model, was uncertain; and
- the estimated rate of patients who relapse and receive second-line therapy (71%, based on market research) and the proportion of patients with WHO scores of two or less ([redacted]% in prevalent patients and [redacted]% in incident patients) was uncertain.

6.17 Overall, the resubmission's estimated expenditure for ibrutinib in MCL was possibly overestimated and uncertain due to the use of a high uptake rate [redacted]%) particularly in the prevalent pool of patients who may have already received multiple lines of treatment, and the uncertain estimates of: treatment duration; rate of patients who relapse and receive second-line therapy; and the proportion of patients with WHO scores of two or less.

6.18 The pre-PBAC response re-iterated that the treatment duration used in the financial estimates (mean duration of [redacted] months) was based on the Kaplan-Meier PFS curves from the key clinical trial (MCL-3001). The pre-PBAC response stated that these data were mature as [redacted]% of ibrutinib patients had progressed or died at the time of the final analysis. Further, the pre-PBAC response stated that the median treatment duration in the named patient program was [redacted] months (underpinning data not provided), which was slightly longer than the median PFS in MCL-3001 of 15.6 months.

6.19 The PBAC noted that the duration of therapy was assumed to be the same in both prevalent and incident patients, and that no evidence had been provided to support this assumption.

6.20 The pre-PBAC response stated that there were no alternative data available on which to base the proportions of patients who relapse and receive second-line therapy and the proportion with WHO scores of two or less.

For more detail on PBAC's view, see section 12 PBAC outcome.

First-line CLL/SLL

7 Requested listing – first-line CLL/SLL

7.1 The resubmission requested the following listing for first-line CLL or SLL.

7.2 Suggestions and additions proposed by the Secretariat to the requested listing are added in italics and suggested deletions are crossed out with strikethrough.

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
IBRUTINIB Capsules 140mg, 90	1	5	$8,782.81[a] (published) $[redacted] (effective)	Imbruvica® JC

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	☒Medical Practitioners
Episodicity:	~~Previously untreated~~
Condition:	Chronic lymphocytic leukaemia (CLL) /Small lymphocytic lymphoma (SLL)
Restriction Level	☒Authority Required – Telephone
Clinical criteria:	The ~~patient~~ condition must be previously untreated AND ~~The treatment must be as monotherapy~~ *The treatment must be the sole PBS-subsidised therapy for this condition* AND ~~The p~~Patient must be inappropriate for ~~fludarabine based therapy~~ treatment with a purine analogue [b] AND Patient must have a WHO performance status ~~score of 2 or less~~ *of 0 or 1* [c] AND ~~Patient must not receive PBS-subsidised ibrutinib if progressive disease develops while on PBS-subsidised ibrutinib~~ *Patient must not develop disease progression while receiving PBS-subsidised treatment with this drug for this condition* [c]
Prescriber Instructions:	A patient is considered unsuitable for treatment with ~~fludarabine based therapy~~ a purine analogue as demonstrated by at least one of the following: a. Age ≥ 70 years b. Age ≥ 65 years and the presence of comorbidities (Cumulative Illness Rating Scale ≥ 6 or creatinine clearance < 70 mL/min) that might place the patient at an unacceptable risk for treatment-related toxicity with purine analogue-based therapy c. History of autoimmune thrombocytopenia d. 17p deletion
Administrative Advice	Special Pricing Arrangements apply No increase in the maximum quantity or number of units may be authorised. No increase in the maximum quantity or number of units may be authorised.

[a] Per Table 1.17, p47 of the resubmission. The economic model used a DPMQ of $[redacted] based on potential rebates from the proposed risk sharing arrangement.

[b] "Fludarabine-based therapy" has been amended to "treatment with a purine analogue" for consistency with the restriction in the relapsed/refractory setting.

[c] Changes were proposed for consistency with the current PBS restriction for ibrutinib in relapsed/refractory SLL/CLL

7.3 The requested price (effective DPMQ of $[redacted]) was the same as per the previous submission (and the same as the effective price in the relapsed/refractory setting). The resubmission assumed that its proposed RSA would reduce the cost to the Commonwealth and applied a lower DPMQ in the economic model of $[redacted]

(a [redacted]% reduction). This was based on rebates that would only be realised if utilisation was at the levels estimated by the resubmission.

7.4 As requested by the PBAC in its previous consideration, the restriction was updated to include a definition of when a patient would be considered unsuitable for treatment with fludarabine-based therapy. The wording was consistent with that previously proposed by the PBAC (PSD, ibrutinib CLL/SLL, November 2017, Paragraph 2.2), which was based on the PBS restriction in the relapsed/refractory setting. This was the only change to the requested restriction compared with the previous submission.

7.5 In its previous consideration, the ESC had noted that there was no definition of progressive disease in the proposed restriction. The PBAC (November 2017) had considered that progressive disease during or after therapy characterised by at least one iwCLL criteria, as per the RESONATE-2 trial protocol, was appropriate (PSD, ibrutinib CLL/SLL, November 2017, Paragraph 2.1).

7.6 The PBAC noted that flow-on changes would be required to the restriction for relapsed/refractory CLL/SLL to specify that patients who have received ibrutinib as first-line therapy are not eligible for PBS-subsidised ibrutinib in the relapsed/refractory setting, thereby restricting ibrutinib use to once in a patient's lifetime.

For more detail on PBAC's view, see section 12 PBAC outcome.

8 Previous PBAC consideration – first-line CLL/SLL

8.1 The outstanding matters of concern to the PBAC for the first-line CLL and SLL indication are summarised in Table 4. In particular, the PBAC previously considered that a resubmission should include (PSD, ibrutinib CLL/SLL, November 2017, Paragraph 7.11):

- a revised economic analysis based on a comparison against rituximab + chlorambucil with a 10-year time horizon and an ICER under $45,000/QALY - $75,000/QALY gained (to take into account the high uncertainty regarding the long-term incremental benefit); and
- revised financial estimates based on updated estimates of the likely incident and prevalent population, and a revised RSA proposal that accounts for the uncertainty in the patient population and estimated duration of therapies.

Table 4: Summary of outstanding matters of concern – first-line CLL and SLL

Component	Matter of concern (November 2017 Minutes)	How the resubmission addressed it
Clinical Evidence		
Proposed PBS restriction	The proposed restriction would require a prescriber instruction to define patients inappropriate for fludarabine-based therapy. [Para 7.3]	PBAC's requested changes were made.
Main comparator	[Para 7.4] The PBAC did not accept the nominated blended comparator of ritux+chl (61.3%), obi+chl (29.4%) and ofat+chl (9.3%). Either non-inferiority to obi+chl and/or superiority of ibrutinib vs ritux+chl would be the most relevant comparisons.	Comparator changed to ritux+chl.
Claim of superiority vs rit + chl	The PBAC considered the resubmission should include updated PFS and OS data if available. The magnitude of long-term benefit was uncertain because of the indolent nature of the disease and hence the small number of clinical events observed in the trials. [Para 7.6 & 7.11]	Updated PFS data were provided, but were not incorporated into the economic model or financial estimates. The updated PFS data resulted in a higher risk ratio for PFS (benefit reducing with longer-term follow-up).
Economic model		
DPMQ	$[redacted] per month (for 1 x 90 capsule bottle)	Unchanged. $[redacted] was used in the model ([redacted]% lower) based on potential RSA rebates. Assumed utilisation thresholds would be met.
Comparator	Base case used a blended comparator. PBAC considered CUA versus ritux+chl would be more informative. [Para 7.9]	Changed to CUA verus ritux+chl only.
Time horizon	Base case: 20 years. PBAC considered 10 years would be more appropriate given immature trial data & patient age[Paras 7.9 & 7.11]	10 years
ICER	Ibrutinib vs weighted comparator: $75,000/QALY-$105,0000/QALY Ibrutinib vs ritux+chl: $75,000/QALY-$105,0000/QALY PBAC considered CUA versus ritux+chl would be more informative with a comparable ICER to obi+chl vs ritux+chl ($15,000/QALY - $45,000/QALY) [Para 7.9]; Resubmission should include a revised economic analysis with ICER < $45,000/QALY - $75,000/QALY [Para 7.11].	Ibrutinib vs ritux+chl: $45,000/QALY-$75,000/QALY (20 year time horizon) and $45,000/QALY-$75,000/QALY (10 year truncated time horizon)
Financial estimates		
Patient numbers	[redacted] over 5 years	[redacted] over 5 years

Component	Matter of concern (November 2017 Minutes)	How the resubmission addressed it
PBS/RPBS cost over 5 years without offsets	Without RSA: more than $100 million High, uncertain and likely underestimated due to: -Failure to include prevalent patients. -Uncertain treatment duration and sequencing. -Potential for use beyond requested indication as there was no definition of "unfit" in the restriction [Para 7.10]. DUSC considered some assumptions to calculate incident pts may be underestimated (assumed [redacted]% of patients with diagnosed SLL/CLL would be treated and [redacted]% of these would be unfit for fludarabine). [DUSC advice Nov 2017, pg 4]	Without RSA: more than $100 million With RSA:more than $100 million ([redacted]% reduction vs without RSA) Changes: -Included prevalent patients; -RSA proposed; but treatment duration [redacted] years) unchanged; - Definition of "unfit" added to restriction Per DUSC advice, incident pts increased to [redacted]% treated and [redacted]% unfit.
PBS/RPBS cost over 5 years with offsets	more than $100 million For cost offsets, 1st-line substituted therapies were: ritux+chl (61.3%), obi+chl (29.4%) and ofa+chl (9.3%). Later-line substituted therapies included ibrutinib in r/r setting.	Without RSA: more than $100 million With RSA:more than $100 million All 1st-line substitution was assumed to be from ritux+chl (per economic analysis), although ofatumumab and obinutuzumab may also be substituted 1st-line.
RSA	PBAC agreed in principle with the proposal to enter a RSA for CLL as a whole, combining 1st-line and R/R CLL/SLL[Para 7.10]	RSA proposed [redacted].

Source: November 2017 PBAC minutes and the resubmission

chl = chlorambucil; CLL = chronic lymphocytic leukaemia; CUA = cost-utility analysis; DPMQ = dispensed price for maximum quantity; ICER = incremental cost-effectiveness ratio; obi = obinutuzumab; ofat = ofatumumab; OS = overall survival; PBAC = Pharmaceutical Benefits Advisory Committee; PBS = Pharmaceutical Benefits Scheme; PFS = progression free survival; QALY = quality-adjusted life year; riuxt = rituximab; R/R = relapsed or refractory; RSA = risk sharing arrangement; SLL = small lymphocytic lymphoma; yrs = years

9 Comparator – first-line CLL/SLL

9.1 For first-line CLL/SLL, the previous submission used a blended (weighted) comparator, comprising: 61.3% rituximab; 9.3% ofatumumab; and 29.4% obinutuzumab (all comparators were in combination with chlorambucil). The November 2017 PBAC considered that either non-inferiority to obinutuzumab and/or superiority to rituximab would be the most relevant comparisons (PSD, November 2017, Paragraph 7.4). To address this, the resubmission changed the comparator to rituximab (+ chlorambucil) only. The PBAC considered this was appropriate.

For more detail on PBAC's view, see section 12 PBAC outcome.

10 Consideration of the evidence– first-line CLL/SLL

Sponsor hearing

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

Consumer comments

10.2 The PBAC noted and welcomed the input from individuals (2) and organisations (1) via the Consumer Comments facility on the PBS website, which related to the use of ibrutinib in CLL/SLL. The comments described the importance of having a range of treatment options available for CLL given the progressive nature of the condition. Lymphoma Australia outlined that the advantages of ibrutinib in CLL/SLL include the less severe adverse event profile compared with alternatives and the convenience of an oral formulation.

Clinical trials

10.3 To address the PBAC's previous concerns about the magnitude of long-term benefit, the resubmission presented longer-term follow-up data for progression-free survival (PFS) from RESONATE-2 (ibrutinib versus chlorambucil). This is shown in Table 5, and was based on a conference abstract, published in December 2017 (no data-cut date provided). This provided three years median follow-up. The previous submission was based on the February 2016 (minimum 24 months follow-up, unknown median duration of follow-up, used in economic model) and May 2015 data-cuts (median 18 months follow-up).

10.4 The resubmission stated that no longer term overall survival (OS) data were available. The resubmission stated that any updated OS data would not address the PBAC's previous concerns regarding the magnitude of long-term benefit due to the large extent of crossover in the trial (41% of patients in the chlorambucil arm of RESONATE-2 crossed over to receive ibrutinib as a subsequent therapy).

Table 5: Summary of results of the indirect comparisons based on investigator-assessed PFS from RESONATE-2: 3 years median follow-up in the resubmission versus 1.5 years (May 2015 data-cut) in the previous submission

Trial	Outcome	Ibr n/N (%)	Chl n/N (%)	Absolute difference	HR (95% CI)
New data presented in resubmission (published December 2017, 35 months median follow-up) [a]					
RESONATE-2 ibr vs. chl	Median follow-up	35.7 months	34.4 months		
	% PFS at 30 months	85%	28%	-	-
	Median months PFS	NE	15	-	**0.13 (0.08, 0.21)**
				Indirect comparison ibr vs. ritux+chl	[redacted]
Data presented in the November 2017 submission					
February 2016 data-cut, unclear duration of follow-up [b] (used in economic model, limited data presented)					
RESONATE-2	Median months PFS	NA		NA	[redacted]
				Indirect comparison ibr vs. ritux+chl	[redacted]
May 2015 data-cut, 18 months follow-up [b]					
RESONATE-2 ibr vs. chl	Median follow-up	18.4 months			
	Progressed	6/136 (4.4%)	64/133 (48.1%)	-	-
	Median months PFS	NR	15 (10.2, 18.9)	-	**0.09 (0.04, 0.17**)
				Indirect comparison ibr vs. ritux+chl	[redacted]
Comparators		**Ritux + chl n/N (%)**	**Chl n/N (%)**	**Absolute difference**	**HR (95% CI)**
CLL11 ritux+chl vs chl	Progressed	NA	NA	-	
	Median months PFS	16.3	11.1	5.2 months	**0.44 (0.34, 0.57)**

Source: Section 6, pp 21-23 of the resubmission; Tables 4 and 5, paragraph 6.11, PBAC Minutes 6.05 ibrutinib (CLL-SLL) MINS 11-2017
Chl = chlorambucil; CI = confidence interval; HR = hazard ratio; ibrutinib = ibrutinib; NA = not available; NE = not estimable; ritux = rituximab; PFS = progression free survival; vs = versus; **bold** = statistically significant.
[a] Limited information were available about the new data (results were only available in abstract form). The date of the data-cut and method of assessment (i.e. investigator-assessed or Independent Review Committee) were unclear.
[b] Based on investigator-assessed PFS.

10.5 With longer follow-up, the hazard ratio (HR) for PFS increased from [redacted] (95% confidence interval (CI): [redacted]) in the February 2016 data-cut, to 0.13 (95% CI: 0.08, 0.21) in the data-cut published in December 2017. The HR for PFS for the indirect comparison increased from [redacted] (95% CI: [redacted]) to [redacted] (95% CI: [redacted]). In its previous consideration, the ESC noted that there was a trend to less favourable indirect comparison results in the updated data, when comparing results from May 2015 to February 2016 (PSD, Paragraph 6.12, ibrutinib CLL/SLL, November 2017).

10.6 These updated data were not used in the resubmission's revised economic evaluation, which continued to be based on a February 2016 data-cut. This may not be conservative given the trend to less favourable results in updated data.

10.7 Further, the financial estimates relied on treatment duration estimates from the economic model. Use of less recent PFS data may have overestimated the treatment duration as treatment is until progression (overestimated the financial impact).

10.8 Updated safety data for ibrutinib were also included in the conference abstract. Safety data for the comparator arm (chlorambucil) were not provided.

Table 6: Prevalence of selected Grade ≥ 3 adverse events over time on ibrutinib

Adverse event, n (%)	0-1 Year (n = 135)	1-2 Years (n = 123)	2-3 Years (n = 111)	3-4 Years (n = 47)
Infections	23 (17%)	9 (7%)	10 (9%)	0
Neutropenia	11 (8%)	4 (3%)	1 (1%)	0
Pneumonia	7 (5%)	3 (2%)	4 (4%)	0
Bleeding	4 (3%)	4 (3%)	1 (1%)	0
Atrial fibrillation	2 (1%)	0	4 (4%)	0

Source: Table 1, Tedeschi et al, 2017 Abstract 1746, ASH 59th Annual Meeting

10.9 In its previous consideration, the PBAC "considered the claim of non-inferior safety to the comparators was supported by the indirect comparisons, but reiterated its concerns that ibrutinib is associated with an increased risk of clinically significant atrial fibrillation" (PSD, ibrutinib CLL/SLL, November 2017, Paragraph 7.8). The updated safety data indicated that the prevalence of atrial fibrillation was highest at 2 to 3 years.

Clinical claim

10.10 For first-line CLL/SLL, the resubmission claimed that ibrutinib had superior comparative effectiveness and non-inferior safety to rituximab + chlorambucil. The PBAC previously (PSD, November 2017) accepted that there was a clinical benefit compared with rituximab + chlorambucil.

10.11 In its previous consideration, the PBAC considered that the claim of non-inferior safety between ibrutinib and the comparators was supported by the indirect comparisons presented in the submission, but noted that emerging data suggested that there is an increased risk of atrial fibrillation associated with ibrutinib (PSD, November 2017, para 6.40). The PBAC noted that the updated data from the RESONATE-2 trial showed that ibrutinib was associated with a 4% risk of Grade 3 or higher atrial fibrillation at 2 to 3 years.

Economic analysis

10.12 For first-line CLL/SLL, the resubmission stated that the following changes were made to the economic model: the comparator was changed to rituximab + chlorambucil (rather than a blended comparator); the time horizon was reduced to ten years

(from 20 years); the cost of ibrutinib was reduced to reflect potential rebates from the proposed RSA; and dispensing fees were updated.

10.13 As a minor submission, changes to the economic model were not evaluated. However examples of other changes included that hospital costs were updated to reflect the 2017-18 National Efficient Price, and the model was amended to enable different ibrutinib costs to be used in the first-line and relapsed/refractory settings. The latter was to address an issue raised in the November 2017 PBAC meeting that the ibrutinib price used in the economic model in the relapsed/refractory setting did not take into account measures implemented to contain risks associated with the cost of ibrutinib to the PBS in that setting.

10.14 As the revised model was not evaluated, the PBAC considered that it was unclear whether the changes made in the re-submission had adequately addressed its previous concerns.

10.15 The results of the economic evaluation, as presented in the resubmission, are outlined in Table 7.

Table 7: Results of economic evaluation: ibrutinib first-line CLL/SLL (10 yr time horizon, RSA included in AEMP [a])

	Ibrutinib	Ritux + Chl	Incremental
Costs			
1st line	$[redacted]	$[redacted]	$[redacted]
Later lines	$[redacted]	$[redacted]	-$[redacted]
Total	$[redacted]	$[redacted]	$[redacted]
Outcomes			
LYs	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICERs			
Cost per LYG			$[redacted]
ICER / QALY with potential RSA rebate (DPMQ of $[redacted] applied in 1st line)			**$[redacted]** [b]
ICER / QALY without RSA (DPMQ of $[redacted] applied in 1st-line)			**$[redacted]** [c]
Previous submission ICER/QALY – ritux + chl as comparator + 10 year time horizon + same cost for ibrutinib in 1st and 2nd line settings			$[redacted] [d,e]

Source: Tables 1.19 and 1.20, p49 of the resubmission

Chl = chlorambucil; DPMQ = dispensed price for the maximum quantity; ICER = incremental cost-effectiveness ratio; LY(G) = life year (gained); QALY = quality-adjusted life year; ritux = rituximab; RSA = risk sharing arrangement; yr = year

[a] In the resubmission, the AEMP was calculated by: [redacted]. For first-line CLL/SLL, this resulted in a [redacted]% reduction to the AEMP ($[redacted]). For relapsed/refractory CLL/SLL this resulted in a [redacted]% reduction to the AEMP ($[redacted])

[b] The pre-PBAC response stated that the ICER was revised to $[redacted]/QALY due to the "changes to the overall financial estimates". The basis for this change was unclear.

[c] With ibrutinib rebates applied in second-line (i.e. DPMQ of $[redacted] in second-line) per the resubmission's base case.

[d] Base case in the previous submission used a 20-year time horizon and weighted comparator for which the ICER was $[redacted]/QALY.

[e] Based on model submitted for November 2017 (dispensing fees and mark-ups were not updated)

10.16 The ICER reduced from $75,000/QALY-$105,000/QALY in the previous submission (when comparable parameters were applied, i.e. a ten-year time horizon and rituximab + chlorambucil as the comparator) to $45,000/QALY-$75,000/QALY in the resubmission due to the assumed rebate resulting from the application of the RSA. The assumed impact of rebates from the RSA was a [redacted]% reduction to the DPMQ for first-line CLL/SLL (DPMQ of $[redacted]) and [redacted]% for relapsed/refractory CLL/SLL (DPMQ of $[redacted]), [redacted].

10.17 The assessment of cost-effectiveness relied on ibrutinib utilisation being at the levels estimated by the resubmission. If utilisation was lower ([redacted]), then the ICER would be higher.

10.18 The resubmission did not present any sensitivity analyses.

10.19 In its previous consideration, the PBAC had considered that a resubmission should include a revised economic analysis with an ICER under $45,000/QALY-$75,000/QALY. In particular, the PBAC considered a comparable ICER to obinutuzumab + chlorambucil from March 2015 ($15,000-$45,000) would be appropriate (PSD, ibrutinib CLL/SLL, November 2017, Paragraph 7.9 and 7.11). The ICER proposed by the resubmission ($45,000-$75,000) was significantly higher than that for obinutuzumab + chlorambucil ($15,000-$45,000). Further, the resubmission's approach of basing the cost of ibrutinib on full application of the RSA introduced considerable uncertainty.

Estimated PBS usage & financial implications

<u>CLL/SLL – first-line</u>

10.20 The PBAC noted that, compared with the previous submission, the resubmission made substantial changes to the financial estimates which could not be evaluated in the context of a minor submission. The PBAC further noted that the pre-PBAC response made additional substantial revisions to the financial estimates, which were not evaluated and that limited information had been provided to substantiate the changes made in the pre-PBAC response.

10.21 At its November 2017 meeting, the PBAC "noted the DUSC advice that the high, uncertain and likely under-estimated financial impact of first-line listing of ibrutinib was driven by the failure to include prevalent patients, and the uncertain treatment duration and sequencing which was based on the economic model" (PSD, ibrutinib CLL/SLL November 2017, Paragraph 7.10). To address these concerns, the resubmission included prevalent patients, increased the number of incident patients and proposed an RSA.

10.22 Changes to the financial estimates, as stated in the resubmission, are outlined in Table 8.

Table 8: Changes in assumptions in the financial estimates for first-line CLL/SLL

	Nov 2017	Resubmission
Inclusion of prevalent patients (per Para 7.10 of PBAC Minutes, Nov 2017)		
Number of prevalent CLL/SLL patients	Not included	10,337
% of prevalent pts who are previously untreated and will be treated in first-line	Not included	16.0%
Uptake	Not included	[redacted]%
% of prevalent patients commencing tx each yr	Not included	[redacted]% per yr in Yrs 1 to 5
Impact: No. of prevalent pts treated over 5 yrs	0	[redacted]
Increasing the incident population (per DUSC advice Nov 2017, page 4)		
% of incident patients treated	[redacted]% (based on r/r setting)	[redacted]%
% of treated patients who are unsuitable for fludarabine in 1st-line	[redacted]% (based on r/r setting)	[redacted]%
Impact: No of incident pts treated over 5 years	[redacted]	[redacted]
Proportions of substituted therapies		
Rituximab + chlor Ofatumumab + chlor Obinutuzumab + chlor	61.3% 9.3% 29.45	Rituximab + chlor: [redacted]%

Source: Table 1.7, p 27 of the resubmission
AIHW = Australian Institute of Health and Welfare; chlor = chlorambucil; CLL = chronic lymphocytic leukaemia; chlor = chlorambucil; DUSC = Drug Utilisation Sub-Committee; no. = number; R/R = relapsed or refractory; SLL = small lymphocytic lymphoma; tx = treatment; yr = year

Patient numbers

10.23 The resubmission estimated almost double the number of patients would be treated, compared with the previous submission ([redacted] patients over five years versus [redacted] in the previous submission). This was because prevalent patients were included and a higher number of incident patients were included (discussed in turn below).

10.24 Prevalent patients were included, based on 31-year prevalence from the Australian Institute of Health and Welfare's 'Cancer in Australia' report (10,337 patients). The resubmission estimated that [redacted]% of these prevalent patients would be previously untreated in first-line and eligible for ibrutinib. This was based on the difference between the proportions of treated patients in the relapsed/refractory ([redacted]%) versus first-line ([redacted]%) settings, which was [redacted]%. Of these patients, [redacted]% were assumed to be unfit for fludarabine-based chemotherapy.

10.25 As a minor resubmission, these changes were not evaluated. Examples of issues identified included (noting this is not an exhaustive list of all potential issues): the resubmission used 31-year prevalence (10,337 patients) which likely included a large proportion of long-term survivors; the rationale for assuming that [redacted]% of prevalent patients (who are previously untreated) would be treated in the first-line setting was unclear (though the methodology was described); the same uptake rate ([redacted]%) was assumed in both prevalent and incident patients; and no justification was provided

for the use of an even proportion of prevalent patients commencing ibrutinib each for the first 5 years of listing. Further, the resubmission's estimates may not have adequately accounted for the eligibility criteria proposed in the restriction (i.e. usage would be restricted to patients with a WHO performance status of 2 or less and who are unsuitable for fludarabine).

10.26 The pre-PBAC response:

- stated that the estimate of 31-year prevalence (10,337 patients) was from 2012, while the number of patients towards the end of 2018 (the time from which the estimates where assumed to start) would likely be higher;
- updated the financial estimates to remove the proportion of patients with a WHO performance status > 2. Per the estimates for MCL, the resubmission assumed that [redacted]% of prevalent patients and [redacted]% of incident patients had a WHO performance status of ≤ 2. The pre-PBAC response stated that the use of these differing proportions justified the use of the same uptake rate in prevalent and incident patients; and
- clarified that the estimates had already accounted for patients unsuitable for fludarabine ([redacted]% based on market research).

10.27 The PBAC noted that the pre-PBAC response did not address all the issues outlined (e.g. the use of an even proportion of prevalent patients commencing ibrutinib in each of the first 5 years of listing).

10.28 The resubmission also estimated that a higher number of <u>incident patients</u> would commence treatment ([redacted] patients over five years) than the previous submission ([redacted]). This was primarily because the proportion of incident patients who would be treated was increased from [redacted]% to [redacted]%. This change was made because the DUSC had previously noted that [redacted]% was also used in the relapsed/refractory setting and was likely to be an underestimate in the first-line setting. The resubmission stated that the updated proportion ([redacted]%) was based on data from the Leukaemia Foundation. The methodology and sources were not evaluated; however in July 2015 DUSC noted that this figure "did not make reference to any studies".

<u>Uptake rate</u>

The PBAC noted that the uptake rate was assumed to be constant regardless of the therapy substituted. The PBAC considered that this may not be appropriate as uptake would likely be influenced by which therapy was being substituted.

<u>Treatment duration</u>

10.29 The PBAC had previously considered that the treatment duration was uncertain as it was based on the economic model which was unlikely to reflect clinical practice (PSD, ibrutinib CLL/SLL, November 2017, Paragraphs 7.10 and 6.55). This was not specifically addressed in the financial estimates, and thus the average treatment

duration remained at [redacted] months (i.e. [redacted] years of ibrutinib treatment), with [redacted]% compliance over this whole duration. Further, the most recent PFS data from RESONATE-2 were not incorporated into the financial estimates. This may have further overestimated utilisation as treatment is until progression and longer-term data indicates a trend to less favourable results.

10.30 The pre-PBAC response stated that as the treatment duration was estimated to be [redacted]months, there would need to be at least a [redacted]% reduction in the extrapolated PFS (and thus the treatment duration) to have an impact on the 5-year financial estimates.

10.31 The PBAC acknowledged the advice from the pre-PBAC response but considered that the estimated treatment duration may not reflect likely clinical practice. The PBAC noted that for relapsed/refractory MCL the pre-PBAC response had referred to treatment duration data from the named patient program. The PBAC considered that similar "real-world" utilisation data for first-line CLL/SLL would be useful for informing the average treatment duration.

Compliance rates

10.32 The PBAC noted that [redacted]% compliance was assumed over the entire treatment duration, and considered that this was overestimated. The PBAC further noted that persistence did not appear to have been accounted for, while 10.4% of patients in the key trial (RESONATE-2) discontinued ibrutinib due to adverse events.

Cost offsets

10.33 The resubmission assumed that cost-offsets in the first-line setting would be based on replacement of rituximab + chlorambucil; while the previous submission had also included substitution of obinutuzumab and ofatumumab. While the updated offsets aligned with the comparator and the economic model, they did not align with clinical practice where some substitution from obinutuzumab and ofatumumab would occur.

10.34 The pre-PBAC response revised the financial estimates to account for substitution of all three regimens, based on the proportions that had been used in the previous submission (which were based on PBS usage data): 61.3% rituximab + chlorambucil; 9.3% ofatumumab + chlorambucil; and 29.4% obinutuzumab + chlorambucil.

10.35 The resubmission estimated offsets for reduced use of ibrutinib in the relapsed/refractory setting in two different parts of the financial estimates using two different methods:

- in the financial estimates for first-line CLL/SLL, where the offsets were based on the sequencing of treatments in later-lines from the economic model; and

- in 'Flow-ons for relapsed/refractory CLL/SLL', which was a specific analysis provided in the resubmission to calculate these offsets (discussed under the next heading).

10.36 The two sets of estimates were not similar (e.g. $[redacted] million of offsets for reduced second-line ibrutinib were estimated in Year 5 in Table 9, versus $[redacted] million in the corresponding year in Table 10, noting there is a one year difference in the starting point of the two sets of estimates).

10.37 The pre-PBAC response acknowledged that two sets of discordant estimates had been provided for reduced use of ibrutinib in the relapsed/refractory setting. The pre-PBAC response removed the offsets estimated in 'Flow-ons for relapsed/refractory CLL/SLL' (i.e. those discussed below and presented in Table 10) stating these were based on outdated inputs. Thus, the pre-PBAC response proposed that the cost offsets for later-line ibrutinib should be based on sequencing of treatments in later-lines from the economic model.

10.38 In its previous consideration (November 2017), the DUSC considered that a key issue of uncertainty was that the treatment sequences and treatment durations were based on the economic model that is not likely to reflect usage and cost in practice (PSD, November 2017, para 6.55).

Estimated cost to the PBS/RPBS

10.39 Table 9 shows the estimated cost to the PBS/RPBS for first-line ibrutinib (without the RSA), as estimated in the resubmission.

Table 9: Estimated cost to PBS/RPBS for ibrutinib in first-line CLL/SLL (without RSA) – per the resubmission

	Year 1 1 Dec 2018	Year 2 1 Dec 2019	Year 3 1 Dec 2020	Year 4 1 Dec 2021	Year 5 1 Dec 2022	Year 6 1 Dec 2023
Number of patients commencing treatment each year						
Incident pts	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prevalent pts[c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total pts initiating ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Previous: Total pts	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Number of packs of ibrutinib (assuming tx duration of 90 months)						
No. ibrutinib packs[d]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Previous sub	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Cost to PBS/RPBS (less copayments)						
Cost to PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Previous sub	$[redacted]	$38,358,719	$[redacted]	$[redacted]	$[redacted]	
Cost-offsets from substituted therapies [e]						
Rit + chlorambucil [a]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
2nd-line ibrutinib [e]	$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
Total cost offsets	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
Previous sub: total	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$40,744,854	
Net cost to PBS/RPBS [b]						
Net cost R/PBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Previous sub	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	

Source: Table 15, 6.05 ibrutinib (CLL-SLL) MINS 11-2017
Assumed DPMA is $[redacted] (effective)
Pt = patients; ritux = rituximab; RSA = risk sharing arrangement; sub = submission
[a] Also includes pegfilgrastim, less copayments. Based on cost of rituximab in January 2018.
[b] The resubmission also assumed there would also be MBS cost-offsets (reduced infusions) of $[redacted] over five years
[c] For derivation of prevalent patients see Paragraph 10.22
[d] Assuming duration of [redacted] months treatment per patient, based on the duration of treatment in the economic model (treat to progression) with [redacted]% compliance over the [redacted] month period.
[e] While revised estimates were provided in the pre-PBAC response, these are not reported in the table given the substantial changes that were not evaluated.

10.40 The resubmission assumed the cost to the PBS/RPBS without offsets would be substantially more than $100 million over five years, which was significantly higher than the previous submission (more than $100 million over five years).

10.41 The net cost to the PBS/RPBS including offsets was estimated in the resubmission to be more than $100 million over five years.

Flow-ons for relapsed/refractory CLL/SLL (from the resubmission; this method was removed in the pre-PBAC response)

10.42 The financial estimates for ibrutinib in relapsed/refractory CLL/SLL (which was recommended by the PBAC in January 2017) did not account for use of ibrutinib in the first-line setting. As the resubmission proposed that patients would only be eligible for PBS-subsidised ibrutinib once in a lifetime, listing in the first-line setting would reduce use in the relapsed/refractory setting.

10.43 Thus, the resubmission conducted a specific analysis to calculate the offsets for reduced use of ibrutinib in the relapsed/refractory setting. The resubmission assumed that the proportion of treated incident patients who would be eligible for ibrutinib in the relapsed/refractory setting would reduce from [redacted]% to [redacted]% in Year 3 onwards due to the listing in first-line. The proportion ([redacted]%) was based on market research (So What Research, 2014). This market research was conducted in 2014, and the resubmission did not justify whether it would reflect current practice.

10.44 The resubmission assumed that it would take patients (who are unsuitable for fludarabine) two years to progress from starting first-line treatment to requiring treatment for relapsed/refractory disease. The resubmission stated this was based on previously agreed financial estimates in relapsed/refractory CLL/SLL. However, the resubmission did not provide relevant clinical data to support this assumption in this setting.

10.45 The resubmission assumed there would be no impact on the prevalent population of relapsed/refractory patients who would be treated with ibrutinib (i.e. the prevalent pool of patients diagnosed prior to 2012).

Table 10: Changes in patient numbers in relapsed/refractory CLL/SLL: previously agreed vs current resubmission

	Year 1 [a] 1 Dec 2017	Year 2 [a] 1 Dec 2018	Year 3 1 Dec 2019	Year 4 1 Dec 2020	Year 5 1 Dec 2021	Year 6 1 Dec 2022
Prevalent patients treated: unchanged [b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incident patients						
Current resubmission [c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Agreed in Jan 2017 [d]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total patients starting ibrutinib in r/r setting						
Current resubmission	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Agreed in Jan 2017	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total packs dispensed in r/r setting						
Current resubmission	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Agreed in Jan 2017	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost to PBS/RPBS (less patient copayments; without RSA)						
Current resubmission	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Agreed in Jan 2017	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Difference (i.e. reduced use due to 1st-line)	$[redacted]	$[redacted]	$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
Net cost to PBS/RPBS/MBS including PBS offsets (without RSA)						
Current resubmission	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Agreed in Jan 2017	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]

Source: Table 1.9, p 32 and Table 1.10, p34 of the resubmission

[a] The years are based on the relapsed/refractory listing (i.e. Year 1 started in December 2017). The resubmission stated that it "anticipated" that PBS listing of ibrutinib for first-line CLL/SLL and MCL would occur in December 2018, which would be Year 2 of the estimates in the relapsed/refractory setting.

[b] Based on [redacted] prevalent patients (based on incidence over 10 years, with survival estimates included); 54% treated; 63% unfit and in the relapsed/refractory setting; [redacted]% uptake. Of the resulting [redacted] patients: [redacted]% would be treated in Year 1; [redacted]% in Years 2 and 3; [redacted]% in Years 4 and 5.

[c] The reduction to [redacted]% eligible commences in Year 4 of listing in the relapsed/refractory setting because the resubmission assumed ibrutinib would be listed first-line in Year 2. Based on the clinician survey: patients who were fit for fludarabine-based therapy in an earlier line, but subsequently progressed and became unfit for fludarabine-based therapy. The proportion appeared to have been miscalculated - it should be [redacted]% rather than [redacted]% because cell B7 in the "Treatment algorithm" worksheet includes fit patients in the third-line setting rather than unfit patients.

[d] Based on the clinician survey: patients who were unfit for fludarabine-based therapy and in the relapsed/refractory setting.

10.46 The resubmission assumed that the total number of treated patients (in the relapsed/refractory setting) would reduce from [redacted] over five years to [redacted] with the listing of ibrutinib in the first-line setting (a reduction of [redacted]%). This estimated reduction was based on market research from 2014 (So What Research, 2014).

10.47 The resubmission estimated that the cost to the PBS/RPBS in Year 6 without offsets (and without the RSA) would be $30-$60 million, versus $30-$60 million in the

previously agreed estimates. Thus, listing of ibrutinib in the first-line setting was assumed to reduce expenditure in the relapsed/refractory setting by $10-$20 million in Year 6. This was significantly less than the corresponding PBS cost-offsets assumed in the first-line estimates (discussed above), which were $30-$60 million in the corresponding year.

10.48 As outlined previously, the pre-PBAC response acknowledged that the offsets for later-line ibrutinib had been estimated using two different methods. The pre-PBAC response stated that it provided revised estimates that removed the estimates outlined above (i.e. Table 10).

For more detail on PBAC's view, see section 12 PBAC outcome.

Risk sharing arrangement (RSA): all indications

[redacted]

10.49 The resubmission proposed an [redacted] RSA for ibrutinib [redacted]

10.50 The resubmission stated that the current RSA for relapsed/refractory CLL/SLL was based on:

- [redacted].
- [redacted]);
- [redacted];
- [redacted]
- [redacted]

[redacted]; and

- [redacted].

10.51 The proposed [redacted]:

- [redacted];
- [redacted].
- [redacted].

10.52 Table 11 outlines the utilisation levels in the RSA proposed by the resubmission. The table shows the [redacted], as shown in Table 12.

Table 11: [redacted]

	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]						
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]						
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]						
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

The above redacted table shows the basis for RSA as proposed in the resubmission.

Table 12: Impact of the RSA proposed by the resubmission [e]

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 1 to 5
MCL						
Cost to PBS/RPBS [a,d]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RSA reimbursement [d]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost to PBS/RPBS with RSA [b, d]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Reduction in expenditure due to RSA (if utilisation is as estimated; used for % reduction to AEMP)						[redacted]
First-line CLL/SLL						
Cost to PBS/RPBS [a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RSA reimbursement	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost to PBS/RPBS with RSA [b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Reduction in expenditure due to RSA (if utilisation is as estimated; used for % reduction to AEMP)						[redacted]
Relapsed/refractory CLL/SLL [c]						
Cost to PBS/RPBS [a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RSA reimbursement	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost to PBS/RPBS with RSA [b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Reduction in expenditure due to RSA						[redacted]
Total combined RSA across all indications						
Cost to PBS/RPBS [a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RSA reimbursement	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost to PBS/RPBS with RSA [b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Reduction in expenditure due to RSA across all indications						[redacted]

Source: Table 1.1.13, p 43 of the resubmission; Table 1.15, p 45 of the resubmission

[a] Ibrutinib cost only, less copayments. Does not include cost-offsets for substituted drugs or MBS savings

[b] Ibrutinib cost only. Does not include cost-offsets for substituted drugs or MBS savings

[c] An RSA is already approved in relapsed/refractory CLL/SLL, which has a cost to the PBS/RPBS with RSA of $[redacted].

[d] Different costs for MCL were reported in Table 1 of the Pre-PBAC response. The patient and prescription numbers for MCL were unchanged between the pre-PBAC response and the resubmission. Thus, the basis for the different costs was unclear

[e] While revised estimates were provided in the pre-PBAC response, these are not reported in the table given the substantial changes that were not evaluated.

10.53 The resubmission stated that the proposed RSA [redacted].

10.54 The rebates leading to the reduced price would only be realised if ibrutinib utilisation was at the level estimated in the resubmission. The PBAC noted that this in turn impacts on the cost effectiveness reasonably expected for each of the indications.

10.55 As a minor resubmission, the changes made since the previous submission were not evaluated. However, examples of some of the issues identified during preparation of the Overview indicated that utilisation was unlikely to reach the levels estimated in the resubmission (utilisation was likely overestimated) because:

- in first-line CLL/SLL, the number of packs per patient and the number of prevalent patients treated were overestimated; and
- in relapsed/refractory CLL/SLL, cost-offsets for first-line use were underestimated (which overestimated the cost of ibrutinib in the relapsed/refractory setting).

10.56 Overall, the changes increased the uncertainty in the financial estimates; the PBAC noted that for assessments of cost-effectiveness to rely on RSA rebates being realised, there would need to be a high level of confidence in the utilisation estimates underpinning the RSA.

10.57 Including offsets, the resubmission estimated the net cost to the PBS/RPBS/MBS of listing ibrutinib would be substantially more than $100 million over five years. The offsets may not be reliable because ibrutinib off-sets in the relapsed/refractory setting were double-counted (refer to Paragraph 10.35). Changes were made in the pre-PBAC response to remove double-counting of offsets in relapsed/refractory CLL/SLL.

10.58 The PBAC noted that the resubmission [redacted]. The PBAC noted that this meant there was potential [redacted]. The PBAC considered that this increased the uncertainty of achieving cost-effectiveness in each indication. Further, the PBAC considered that there were significant uncertainties with the utilisation estimates [redacted] would increase the overall financial uncertainty for the Commonwealth.

10.59 The resubmission also requested a Special Pricing Arrangement (published versus effective price) with the same published price per tablet across all three indications.

For more detail on PBAC's view, see section 12 PBAC outcome.

11 PBAC Outcome

Relapsed/Refractory Mantle Cell Lymphoma

11.1 The PBAC recommended extending the PBS-listing of ibrutinib as an Authority Required benefit to include the treatment of patients with relapsed/refractory MCL. The PBAC considered that the cost-effectiveness of ibrutinib in relapsed/refractory MCL was acceptable at the price applied in the economic model. The PBAC considered that effective controls would be needed to ensure this price is realised and to limit the financial costs to the PBS. The recommendation reflected the high clinical need in a condition that affects a small number of patients.

11.2 The PBAC was satisfied that, in relapsed/refractory MCL ibrutinib provides, for some patients, a significant improvement in efficacy over R-CHOP and a reduction in toxicity versus active treatment with R-CHOP.

11.3 The PBAC re-iterated the high clinical need for additional effective and well tolerated treatments for relapsed/refractory MCL.

11.4 The PBAC considered that a grandfathering restriction would be appropriate for patients in the named patient program with stable or responding disease.

12 The PBAC noted the pre-PBAC response's claim that a scenario-based ICER range would provide a more appropriate estimation of the cost-effectiveness of ibrutinib in MCL, rather than basing the ICER on a single, more conservative scenario. However, the PBAC recalled its previous consideration that three of the four proposed scenarios were optimistic and/or uncertain as they assumed that the overall survival curves did not converge within the model time horizon and/or were based on adjusted trial results (PSD, November 2017, para 7.6). The PBAC considered that there was no basis to support a change to its previous consideration, and re-iterated that Scenario 4 provided the most appropriate estimate of the cost-effectiveness of ibrutinib in MCL. The PBAC considered this was particularly appropriate, given it had previously considered that Scenario 4 reflected optimistic assumptions, and that the resubmission had introduced additional uncertainties as the ICER was based on RSA rebates.

12.1 The PBAC considered that the ICER estimated in Scenario 4, $75,000/QALY-$105,000/QALY (per the resubmission), was high. However, given the clinical need in relapsed/refractory MCL, the PBAC considered that the cost-effectiveness of ibrutinib was acceptable at the price applied in the economic model. The PBAC noted that this price was lower than the requested effective DPMQ on the basis that the difference would be rebated through the RSA. The PBAC further noted that this relies on utilisation being at the levels estimated by the resubmission. The PBAC considered that the RSA would need to provide a reasonable level of certainty that

the price applied in the economic model, and thus the estimated cost-effectiveness, would be achieved.

12.2 The PBAC noted that, compared with the previous submission, the only change to the financial estimates was that the uptake rate was reduced from [redacted]% to [redacted]%. This uptake rate was applied to the patient group with a WHO performance status of ≤ 2, to both prevalent and incident patients. This had the effect that fewer prevalent patients were estimated to receive therapy, since prevalent patients would be less likely to receive active therapy based on performance status. The PBAC considered that, in this case, this had sufficiently addressed its previous concerns about the use of the same uptake rate in prevalent and incident patients.

12.3 Overall, the PBAC considered that utilisation was possibly over-estimated particularly in the prevalent patient population. However, the PBAC also considered that there were a lack of alternative reliable data on which to base the estimates and that further robust information was unlikely, in the context of a condition that affects a relatively small number of patients and for which there is a lack of alternative treatment options.

12.4 The PBAC advised that an RSA for MCL was necessary to achieve cost-effectiveness and to minimise the risks associated with the uncertain patient population. The PBAC considered that the RSA should be based on the subsidisation caps proposed in the resubmission for MCL. Given its concerns that utilisation was possibly over-estimated, the PBAC also considered that actual utilisation for this indication (including treatment duration and the number of patients) should be monitored to ensure that cost-effectiveness would be reached.

12.5 The PBAC advised that the limited treatment options available for this patient group and the overall small financial implications to the PBS were important considerations in its decision to recommend ibrutinib for MCL, despite the high and uncertain ICER and the uncertain patient population.

12.6 The PBAC advised that ibrutinib is not suitable for prescribing by nurse practitioners.

12.7 The PBAC recommended that the Early Supply Rule should apply for ibrutinib in relapsed/refractory MCL.

12.8 The PBAC considered that ibrutinib should not be treated as interchangeable on an individual patient basis with any other drugs under Section 101 (3BA) of the *National Health Act 1953*.

<u>First-line CLL/SLL</u>

12.9 The PBAC did not recommend the listing of ibrutinib for the treatment of first-line CLL/SLL on the basis of: uncertain cost-effectiveness given the pricing arrangements proposed; and overestimated financial estimates. The PBAC noted that the cost of ibrutinib applied in the economic model, and thus the ICER, relied on RSA rebates.

The PBAC considered it was unlikely that the rebates would be achieved, and therefore it was unlikely that acceptable cost effectiveness would be realised, as the utilisation underpinning the RSA was significantly overestimated.

12.10 The PBAC noted the consumer comments describing the importance of having a range of treatment options available for CLL. However the Committee re-iterated its previous consideration that for most patients, there are other effective first-line therapies available and that ibrutinib is PBS-listed in relapsed/refractory CLL/SLL.

12.11 The PBAC considered that the proposed restriction should be amended to: include a definition of progressive disease per the RESONATE-2 trial; restrict ibrutinib use in CLL/SLL to once in a patient's lifetime; and to include separate restrictions for initial and continuing treatment.

12.12 The PBAC noted that more recent data were available from the key trial of ibrutinib in first-line CLL (RESONATE-2) which increased the PFS hazard ratio for the indirect comparison of ibrutinib versus rituximab + chlorambucil from [redacted] (95% CI: [redacted], [redacted]) in the previous submission to [redacted] (95% CI: [redacted], [redacted]). The PBAC considered that it would be informative for the economic model and financial estimates to incorporate the updated data given the economic model's reliance on PFS and extrapolated data, and the considerably longer duration of follow-up available with the new data which in turn informs the financial estimates.

12.13 In its previous consideration, the PBAC considered that the claim of non-inferior safety between ibrutinib and the comparators was supported by the indirect comparisons, but noted that emerging data suggest that there is an increased risk of atrial fibrillation associated with ibrutinib (PSD, November 2017, para 6.40). The PBAC considered that the updated data from the RESONATE-2 trial further supported its previous concerns about the risk of atrial fibrillation.

12.14 The PBAC noted that the ibrutinib costs applied in the economic analyses were [redacted]% lower than the requested effective DPMQ on the basis that this difference would be rebated through the RSA. The potential impact of RSA rebates reduced the ICER from $75,000/QALY-$105,000/QALY (without the RSA) to $45,000/QALY-$75,000/QALY (with the RSA). The PBAC noted that the ICER would only be achieved if utilisation was as estimated. For assessments of cost-effectiveness to rely on RSA rebates, the PBAC advised that it would need to have a high level of confidence in the utilisation estimates underpinning the RSA. For first-line CLL/SLL, the PBAC considered that there was substantial uncertainty in the financial estimates that had been provided.

12.15 The PBAC noted that, compared with the previous submission, the resubmission made substantial changes to the financial estimates which could not be evaluated in the context of a minor submission. The PBAC further noted that the pre-PBAC response made additional substantial revisions to the financial estimates, which

were not evaluated and that limited information had been provided to substantiate these changes.

12.16 The PBAC noted that the estimated patient numbers had doubled compared with the previous submission. Overall, the PBAC considered that the financial estimates were substantially overestimated because the patient numbers, uptake rate and compliance rate were overestimated and/or uncertain. For example the PBAC considered that:

- the uptake rate would differ depending on the therapy being substituted, which had not been incorporated into the financial estimates. Further, the PBAC considered that uptake may be affected by the risk of atrial fibrillation.
- the compliance rate (%) was overestimated particularly as it was applied constantly over the month treatment duration. Further, the PBAC noted that the compliance rate did not appear to account for patients discontinuing due to adverse events.
- the substitution and cost-offsets applied in the financial estimates were unclear and limited information was provided to substantiate these estimates.

12.17 The PBAC considered that any resubmission would need to be a major submission and should (i) update the economic model and financial estimates based on the most recent data-cut; (ii) address any outstanding concerns from the PBAC's previous consideration, noting that the substantial changes made in the resubmission and the pre-PBAC response were not evaluated; and (iii) revise the financial estimates to address the overestimated patient numbers and uptake rate, and the uncertain treatment duration, substitution and cost offsets.

12.18 The PBAC considered that, as the ICER relied on the utilisation estimates, the Committee would require a high degree of confidence in the revised utilisation estimates, particularly in the context of the high financial implications and the availability of other treatment options. For the same reasons, the PBAC also considered that an updated RSA would need to propose mechanisms to address , and b) the conceivable event that cost effectiveness is not achieved due to utilisation being different to that proposed. This means the development of a mechanism to ensure that financial expenditure , so that cost effectiveness of each condition is achieved.

12.19 The PBAC considered that the cost-effectiveness of ibrutinib in first-line CLL/SLL is uncertain due to the reliance on extensive extrapolation of the clinical data and the reliance on the RSA. The PBAC therefore considered mechanisms to provide updates to the clinical data (trial or real-world) to ensure the ongoing cost-effectiveness of ibrutinib may be appropriate.

12.20 The PBAC noted that this submission is not eligible for an Independent Review as a positive recommendation had been made for MCL.

Outcome:
Recommended for relapsed/refractory MCL.
Rejected for first-line CLL/SLL.

13 Recommended listing

13.1 Amend existing/recommended listing as follows:

Name, restriction, manner of administration and form	Maximum Qty (units)	No. of Rpts	Proprietary name and manufacturer
Ibrutinib, 140 mg, capsule, 120	1	5	Imbruvica ® Janssen-Cilag Pty Ltd

Category/program:	GENERAL – General Schedule (Code GE)
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
PBS Indication:	Mantle cell lymphoma
Restriction level/method	☒Authority Required – Telephone
Initial treatment	
Treatment phase	Initial treatment
Clinical criteria	The condition must have relapsed or be refractory to at least one prior therapy AND Patient must have a WHO performance status of 0 or 1 AND The treatment must be the sole PBS-subsidised therapy for this condition AND Patient must not have previously received PBS-subsidised treatment with this drug for this condition
Administrative advice	Special Pricing Arrangements apply No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised.
Continuing treatment phase	
Treatment phase	Continuing treatment
Clinical criteria	The treatment must be the sole PBS-subsidised therapy for this condition AND Patient must have previously received PBS-subsidised treatment with this drug for this condition, AND Patient must not develop disease progression while receiving PBS-subsidised treatment with this drug for this condition
Administrative advice	Special Pricing Arrangements apply No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised.

Grandfathering treatment	
Treatment phase	Initial treatment
Clinical criteria	Patient must have previously received non-PBS-subsidised treatment with this drug for this condition prior to [listing date] AND Patient must have a WHO performance status of 0 or 1 AND The treatment must be the sole PBS-subsidised therapy for this condition. AND Patient must not develop disease progression while receiving PBS-subsidised treatment with this drug for this condition.
Administrative advice	Special Pricing Arrangements apply No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised.

14 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.

15 Sponsor's Comment

The sponsor had no comment.