11.03 ZANUBRUTINIB, Capsule 80 mg Brukinsa®, BEIGENE AUS PTY LTD

1 Purpose of Submission

1.1 The Category 3 submission requested the PBAC to revise the previously estimated utilisation of zanubrutinib (Brukinsa®) for the treatment of Waldenström macroglobulinemia (WM).

1.2 The submission proposed an increase to the subsidisation caps for the current risk sharing arrangement (RSA) from Year 3 onwards to reflect the following changes in the utilisation model:

- Increasing the incidence rate from 0.37 to 0.60 per 100,000 population.
- Increasing the prevalence rate from 1.22 to 3.21 per 100,000 population.
- Increasing the proportion of patients assumed to survive to second line treatment from 90% to 100%.

1.3 The current and proposed caps are summarised in Table 1. The submission estimated the additional PBS/RPBS expenditure associated with the revised RSA versus the existing RSA to be [redacted] over 3 years.

Table 1: Proposed subsidisation caps for forward years (Years 3, 4 and 5)

	Y3 (July 2024-June 2025)	Y4 (July 2025-June 2026)	Y5 (July 2026-June 2027)
Current caps ($)	[redacted]	[redacted]	[redacted]
Proposed caps ($)	[redacted]	[redacted]	[redacted]
% increase from existing caps	[redacted]	[redacted]	[redacted]
Maximum additional cost to PBS/RPBS ($)	[redacted]	[redacted]	[redacted]
Revised proposed caps ($)	[redacted]	[redacted]	[redacted]
% increase from existing caps	[redacted]	[redacted]	[redacted]
Maximum additional cost to PBS/RPBS ($)	[redacted]	[redacted]	[redacted]

Source: Table 2.13, p17 of the submission

Note: Revised subsidised caps were calculated by applying the proposed changes and updating other parameter values (i.e., affected medicine costs; Administration, Handling and Infrastructure Fee (AHI Fee); dispensing fees; and patient contributions) and the effective Dispensed Price for Maximum Quantity (DPMQ) of zanubrutinib as of February 2024.

Italics in grey shading represent information provided in the pre-PBAC response but not evaluated.

2 Background

2.1 Zanubrutinib is currently listed on the PBS as a General Schedule Authority Required (Telephone/Online) listing for the treatment of WM in two patient subpopulations: (i) treatment-naïve (TN) patients who are unsuitable for chemo-immunotherapy and

(ii) relapsed/refractory (R/R) patients who have received at least one prior chemo-immunotherapy.

2.2 Zanubrutinib is also listed on the PBS as:

- a General Schedule Authority Required (Telephone/Online) listing for mantle cell lymphoma.
- a General Schedule Authority Required (Telephone/Online) listing for Chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL).

Previous PBAC consideration

2.3 Zanubrutinib was previously considered for WM by the PBAC in July 2021 and March 2022, and was recommended at its March 2022 meeting.

2.4 The previous submissions used an epidemiological approach to estimate the financial impact of listing zanubrutinib. In July 2021, the PBAC considered that the financial impact was likely underestimated, noting the number of patients receiving zanubrutinib (due to underestimating the number of eligible patients and uptake) and the duration of treatment were likely underestimated (paragraph 7.15, zanubrutinib, Public Summary Document (PSD), July 2021).

2.5 On 6 September 2021, a Facilitated Resolution Pathway workshop was held for zanubrutinib to explore feasible options to address outstanding issues raised during the July 2021 PBAC consideration (paragraph 6.47, zanubrutinib, PSD, March 2022).

2.6 In March 2022, the resubmission revised the financial estimates in terms of the prevalent patient population, uptake, PBS cost offsets and costs of bleeding events. The pre-PBAC response further updated the estimated number of grandfathered patients and the treatment durations in response to the Economic Sub-Committee (ESC's) advice that the treatment durations in the economic evaluation and financial estimates should be consistent. Overall, the PBAC considered that the financial estimates informed by the patient numbers in the resubmission and average treatment durations from the economic model were a reasonable basis for an RSA (paragraph 7.7, zanubrutinib, PSD, March 2022).

2.7 A summary of the key parameters in the utilisation and financial estimates considered by the PBAC at its March 2022 meeting is provided in Table 2.

Table 2: Summary of key parameters considered by the PBAC at its March 2022 meeting

Description	Method/Value	March 2022 PBAC consideration
Incidence rate	Estimated a WM incidence of 0.37 per 100,000 (AIHW 2017, Code C88 stated).	The WM incidence could not be verified as Code C88 in the AIHW 2017 data referred to immunoproliferative cancers but did not specify the WM subset (Table 22, zanubrutinib, PSD, March 2022).
Prevalence rate for second line or later (2L+) use in Year 1	For Year 1, a prevalence rate of 1.22 per 100,000 was estimated for the WM subtype, assuming that 1.5% of 5-year prevalence of NHL (19,691) (AIHW 2021, Code C82-86) was WM.	A prevalence rate of 1.22 was the midpoint of the high and low prevalence scenarios of 1.34 and 1.10, noting the Lymphoma Australia reference that only 1 or 2 people (1-2%) in every 100 people with NHL have WM. However, the underlying source that informed the Lymphoma Australia assumption was not available at that time.
Time on treatment	Treatment durations were estimated to be 37.5 and 37.1 months in the TN and R/R populations, respectively, with a [redacted]-month financial stopping rule applied.	Treatment durations were determined as per the ESC's advice that the duration of treatment should be consistent between the models and financial estimates. The treatment duration in the economic models was approximately 37 months as this accounted for discontinuations. (paragraph 6.80, zanubrutinib, PSD, March 2022).
Uptake rate	Estimated an uptake rate of 95% in Years 4-6, assuming patient preference for oral therapy according to sponsor's market research.	It was considered reasonable, given the indolent nature of the disease, patients are likely to cycle through all available treatments during their lifetimes. Therefore, patients might choose an alternative treatment initially but go on to zanubrutinib as a later line (Table 22, zanubrutinib, PSD, March 2022).
PBS cost offsets	Treatment cost offsets included in the resubmission were filgrastim (associated with neutropenia treatment), cyclophosphamide (5% IV and 14% oral R/R regimens), and chlorambucil (16% TN regimens).	Removed non-PBS subsidised treatment in response to the July 2021 PBAC consideration that PBS cost-offsets for bendamustine and rituximab were inappropriate, given these therapies were not PBS-listed (paragraph 7.15, zanubrutinib, PSD, July 2021).
Costs of bleeding events	MBS item 13706 ($86.70, 80% fee) was included in the resubmission as the cost for bleeding events.	The resubmission used the ASPEN[a] data as annual incidence of major haemorrhage while receiving treatment. Cost of major haemorrhage appeared low, but likely to be a hospitalisation cost (Table 22, zanubrutinib, PSD, March 2022).

Source: compiled by the Secretariat during the evaluation; zanubrutinib, Public Summary Document (PSD), March 2022 PBAC meeting
Abbreviations: The Australian Institute of Health and Welfare (AIHW); NHL=non-Hodgkin lymphoma; 2L=second line treatment, R/R=relapsed/refractory, TN=treatment naïve, MBS=Medicare Benefits Schedule
[a] ASPEN: a Phase 3, Randomized, Open-Label, Multicenter Study Comparing the Efficacy and Safety of the Bruton's Tyrosine Kinase (BTK) Inhibitors BGB-3111 and Ibrutinib in Subjects with Waldenström Macroglobulinemia (WM). Clinical Study Report BGB-3111-302

Current RSA and expenditure

2.8 At its March 2022 meeting, the PBAC considered it was unlikely that the patient numbers had been overestimated and thus considered, provided the expenditure caps were based on the average (not maximum) treatment durations from the economic models and the rebate for use above the expenditure caps was [redacted]%, that a cost-effective price would likely be achieved using an RSA (paragraph 7.6, zanubrutinib, PSD, March 2022).

2.9 The submission noted that the PBAC acknowledged there were no PBS-listed therapies specifically for WM, while chemo-immunotherapy was considered as standard treatment at the time of PBAC consideration of zanubrutinib. Given the rarity of WM,

the submission highlighted that its epidemiology and treatment patterns were not well defined due to the absence of an Australian disease registry or specific PBS-subsidised treatment for this patient population.

2.10 The submission stated that the actual zanubrutinib utilisation for the treatment of WM has been higher than the estimated utilisation since it was PBS-listed on 1 July 2022. The actual Commonwealth payment[1] was [redacted] in Year 1 (1 July 2022 to 30 June 2023), while the subsidisation cap was [redacted], and the Commonwealth payment was [redacted] in the first seven months of Year 2, which is higher than the subsidisation cap for Year 2 of [redacted]. This is outlined in Table 3.

Table 3: Zanubrutinib RSA subsidisation caps and Commonwealth Payments since PBS listing

	Date range	RSA Subsidisation Cap	Commonwealth Payment
Year 1	July 2022 to June 2023	$[redacted]	$[redacted][a]
Year 2	July 2023 to June 2024	$[redacted]	$[redacted] (actuals; July 2023 to January 2024)[b] $[redacted] (estimates for 12 months, based on the July 2023 to January 2024 actuals)

Source: Table 1.1, p4 of the submission

[a]. PBS Rebate Management Service - Reimbursement Calculation Report, Deed Commonwealth Payment, dated 1/8/2023

[b]. PBS Rebate Management Service - Reimbursement Calculation Report, Special Pricing Arrangement, months July 2023 to January 2024

3 Requested listing

3.1 The submission proposed no changes to the existing listing. Therefore, the full restrictions have not been included here.

4 Consideration of the evidence

Sponsor hearing

4.1 There was no hearing for this item.

Consumer comments

4.2 The PBAC noted that no consumer comments were received for this item.

Revised utilisation estimates

New epidemiological data

4.3 The submission stated that blood cancer data as published by the Australian Institute of Health and Welfare (AIHW) were only available within the International Classification of Diseases 10th Revision (ICD-10) framework at the time of PBAC consideration for zanubrutinib. The smallest AIHW published grouping available was Code C88, which was 'Immunoproliferative Cancers'. WM belonged in this group as did marginal zone lymphoma (MZL, C88.4). It was unknown what proportion of Code

[1] Commonwealth payment = the total subsidy paid by the Commonwealth (Commonwealth Expenditure) - any amount paid or payable to the Commonwealth under a special pricing arrangement in relation to the supply during that Year (calculated by reference to the number of processed prescriptions) of the drug.

C88 was WM, MZL or others. As such, it was noted that AIHW Code C88 referred to immunoproliferative cancers, but did not specify the WM subset in the March 2022 consideration (Table 22, zanubrutinib, PSD, March 2022).

4.4 In August 2023, the AIHW published comprehensive cancer statistics, including incidence and survival data, providing a more detailed understanding of cancer subtypes for the period of 2003 – 2019 (AIHW 2023a). These new data allowed for the identification of individual haematological subtypes, such as WM. Based on the new data specific to the WM subset, an analysis was conducted to evaluate the potential underestimation of utilisation in the previous submission, which was likely due to underestimated disease incidence and prevalence rates. The submission claimed that the analysis provided evidence to support higher actual utilisation than previously estimated.

4.5 The pre-PBAC response provided results of studies (Talaulikar et al., 2023 and Nguyen et al., 2024) on the incidence and prevalence of WM in Australia based on all WM cases from January 2009 to December 2018 in Victoria, Tasmania, Australian Capital Territory, and Queensland extracted from the Australian cancer registry database[2] as supplementary evidence. The pre-PBAC response noted that the sponsor was involved in these studies.

Revised incidence

4.6 In March 2022, the incidence rate of 0.37 per 100,000 population for WM could not be verified due to the absence of reliable Australian data specific to the WM subset (see paragraph 4.3). To support this incidence base case, the sponsor provided a rationale that the incidence of WM could be derived using the AIHW 2017 data indicating the incidence of non-Hodgkin lymphoma (NHL) in Australia (19.8 per 100,000) and assuming WM accounted for 1 - 2% of NHL cases (Lymphoma Australia[3]). However, it was unknown where Lymphoma Australia sourced the estimate of 1 - 2% (paragraph 6.83, zanubrutinib, PSD, March 2022).

4.7 The submission proposed to update the incidence rate of WM from 0.37 to 0.60 per 100,000 population, based on recent AIHW data (AIHW 2023a). This is the midpoint between the incidence rates in 2017 (0.5 per 100,000, lower estimate) and 2018 (0.7 per 100,000, higher estimate), as outlined in Table 4. The pre-PBAC response stated that the incidence rate of 0.6 in 2019 was chosen, as it was the most recent available data, and equal to the average rate from the preceding three-year period (2017-2019).

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[2] Dipti Talaulikar, Lan Gao, Dieu Nguyen et al. (2023) Incidence, prevalence, and mortality of Waldenström macroglobulinemia (WM) in Australia. Accessed on 14 June 2024 at: https://www.beigenemedical.com/CongressDocuments/Talaulikar_RWE_WM_BLOOD_Abstract_2023.pdf

[3] Lymphoma Australia. (2023). "Waldenstrom's Macroglobulinemia". Accessed on 8 March 2024 at: https://www.lymphoma.org.au/types-of-lymphoma/non-hodgkin-lymphoma/indolent-slow-growing-b-cell-nhl/waldenstroms-macroglobulinemia-wm/

Table 4: Incidence of WM in Australia as published by AIHW for the period of 2015-2019

Year	Incidence	Incidence rate per 100,000 population
2019	149	0.6
2018	177	0.7
2017	134	0.5
2016	121	0.5
2015	118	0.5

Source: Table 2.2, p7 of the submission, AIHW; Cancer Data in Australia: Blood Cancer Survival by histology (AIHW 2023a)
Abbreviation: WM=Waldenström macroglobulinemia

4.8 The pre-PBAC response stated that the age-standardised incidence rates (ASRs) of 0.42 to 0.78 per 100,000 population in Talaulikar 2023 is comparable to the AIHW rates of 0.4 to 0.7 per 100,000 in the same period. The pre-PBAC response argued that, based on Talaulikar 2023 projecting the Australian ASR to rise to 1.4 per 100,000 by 2038, the proposed flat incidence rate of 0.6 per 100,000 population over time is likely a conservative estimate, accounting for the increasing aging population.

Revised prevalence

4.9 The resubmission in March 2022 used a prevalence rate of 1.22 per 100,000 to estimate the prevalent population for second line or later (2L+) use in Year 1. The five-year prevalence rate of 1.22 per 100,000 for WM was derived from a five-year prevalence of 19,691 cases for NHL (AIHW 2021, Code C82-86), assuming that 1.5% of these cases were the WM subtype.

4.10 The submission stated that, like the incidence rate, the five-year prevalence rate of 1.22 per 100,000 for WM in the previous submission was unlikely accurate using the Lymphoma Australia data, which was from an unknown source. Further, the NHL grouping of ICD-10 codes as published by the AIHW included C82 - C86, while WM was C88. This means the five-year prevalence rate of WM applied in March 2022 did not include WM patients.

4.11 The submission presented updated assumptions that differed from the previous submission to estimate a prevalence rate for WM, as outlined below:

a. Change from five-year to ten-year prevalence

- The submission referred to Maqbool 2020[4], which noted that "at least 25% of patients are asymptomatic at presentation and half of them will not require therapy for at least 3 years. However, only 13% of patients with asymptomatic WM are treatment free at 10 years after diagnosis". As such, the submission anticipated that 37% (50% - 13%) of asymptomatic patients would require

[4] Maqbool G, Tam C, et al. A practical guide to laboratory investigations at diagnosis and follow up in Waldenström macroglobulinaemia: recommendations from the Medical and Scientific Advisory Group, Myeloma Australia, the Pathology Sub-committee of the Lymphoma and Related Diseases Registry and the Australasian Association of Clinical Biochemists Monoclonal Gammopathy Working Group, *Pathology* 2020; 52(2): 167–178.

treatment between four and ten years after diagnosis. The evaluation noted this is not an estimate of disease prevalence but of treated prevalence or uptake.

- The submission stated that Maqbool 2020 provided evidence that excluding patients diagnosed more than five years ago from the prevalent population would likely result in an underestimation of PBS utilisation. Therefore, the updated model used a ten-year prevalence rate to calculate the prevalent population, rather than the previously used five-year prevalence rate.

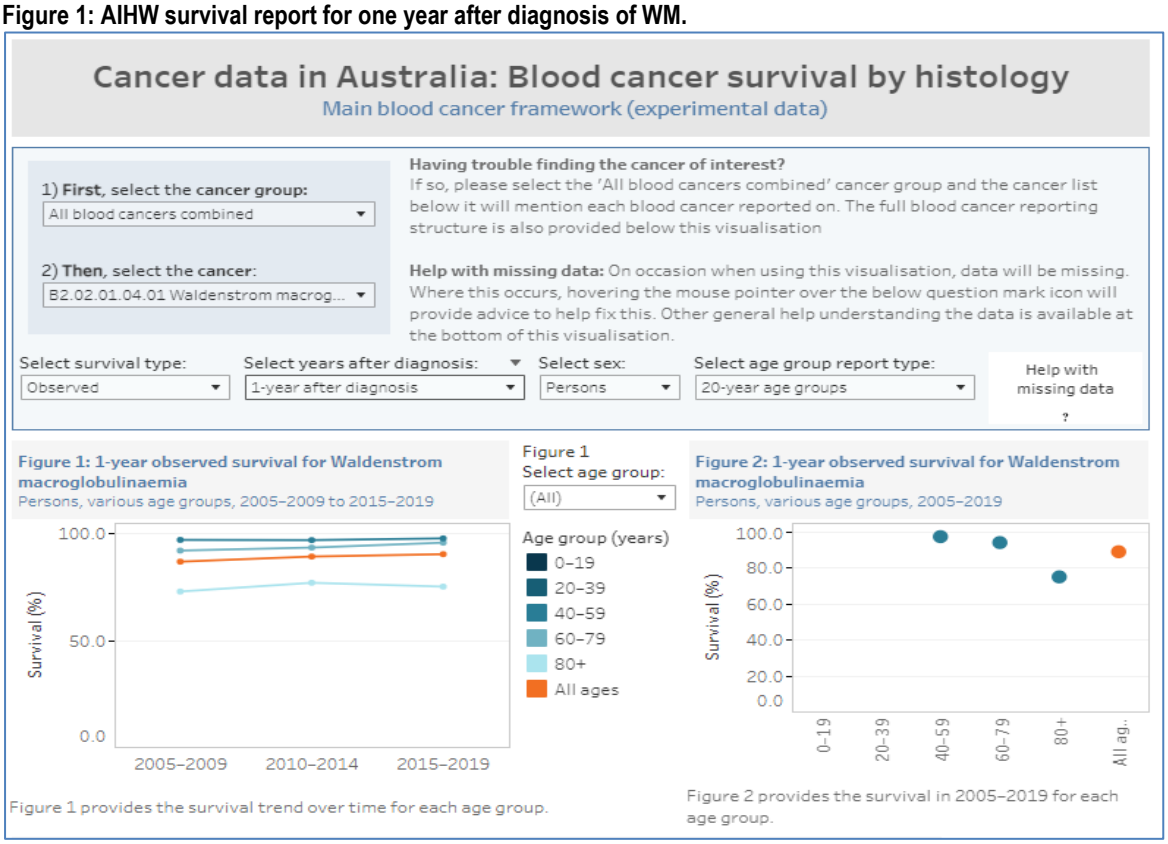
b. Calculating prevalence from incidence and observed survival

- The submission estimated prevalence from incidence and observed WM survival rates (how many WM patients are alive at a certain point in time) published by the AIHW (Figure 1, AIHW 2023a), which provides survival rates up to five years annually after diagnosis, with the most recent period being 2015 - 2019. To calculate a ten-year prevalence, the survival for Years 6 - 10 were taken from the overall survival of those diagnosed with WM between 2001 and 2010 as recorded within the United States SEER database (Castillo et al., 2015[5]). The evaluation indicated that it is uncertain whether the survival rates from the SEER database would accurately reflect those of Australian patients, and the submission could have used a more recent study based on data from the SEER database (Yin et al., 2020[6]), which reports lower survival rates for WM at 5 years (64.4%) and 10 years (42.2%) than presented in Table 5 below.
- 818 patients diagnosed with WM in the previous ten years (2010 – 2019) were estimated to be alive as of 31 December 2019 (Table 5). This was calculated by applying the one-year observed survival rate to the 2019 incidence (the most recent year of available incidence data), the two-year observed survival rate to the 2018 incidence until the tenth year, and then summing these values.
- The ten-year prevalence of 3.21 per 100,000 population was calculated as 818 patients divided by the Australian population of 25,522,169 as of 31 December 2019 (the most recent year in the model), as shown in Table 6.

[5] Castillo J, Olszewski A, et al. Overall survival and competing risks of death in patients with Waldenström macroglobulinemia: an analysis of the Surveillance, Epidemiology and End Results database; *Br J Haematol* 2015;169(1): 81-9.

[6] Yin X, Chen L, et al. Trends in incidence and mortality of Waldenström macroglobulinemia: A population-based study. Front. Oncol. 10:1712.

Figure 1: AIHW survival report for one year after diagnosis of WM.



Source: Figure 2.1, p9 of the submission, the AIHW, Cancer Data in Australia: Blood Cancer Survival by histology (AIHW 2023a)
Abbreviation: WM=Waldenström macroglobulinemia

Table 5: WM ten-year prevalence in Australia as of 31 December 2019

Year	Incidence[a]	Years since diagnosed	Observed survival	Patients alive as of 31 December 2019
2019	149	1	90.3%[b]	135
2018	177	2	84.3%[b]	149
2017	134	3	78.6%[b]	105
2016	121	4	74.0%[b]	90
2015	118	5	69.5%[b]	82
2014	114	6	59.6%[c]	68
2013	96	7	55.6%[c]	53
2012	99	8	50.7%[c]	50
2011	91	9	47.4%[c]	43
2010	96	10	44.8%[c]	43
Total	**1,195**		**68.5%**	**818**

Source: Table 2.3, p10 of the submission
[a] AIHW, Cancer Data in Australia: Blood Cancer Incidence by histology (AIHW 2023a)
[b] AIHW, Cancer Data in Australia: Blood Cancer Survival by histology (AIHW 2023a)
[c] SEER database, WM patients diagnosed between 2001 and 2010 (Castillo et al., 2015)

Table 6: WM ten-year prevalence rate in Australia as of 31 December 2019

Year	Ten-year prevalence (Table 5)	Australian Population 2019	Crude ten-year prevalence rate	Crude ten-year prevalence rate per 100,000 population
2019	818	25,522,169[a]	0.0000321	3.21

Source: Table 2.4, p10 of the submission

[a]. National, state and territory population, reference period 2019 (Australian Bureau of Statistics 2019)

4.12 The pre-PBAC response noted that, while Yin 2020 was published more recently than Castillo 2015, the survival rates in Yin 2020 were based on data from the period of 1980 to 2016, whereas Castillo 2015 covered 2001 to 2010. The sponsor considered that the survival rates from earlier decades were less relevant because patients diagnosed before 2000 are less likely to be alive and thus eligible as prevalent patients, and the five-year survival rates have significantly increased over time.

4.13 The pre-PBAC response also presented a comparison of survival rates from multiple sources to support the claim that survival rates are comparable in Australian and US SEER data. The sponsor further provided the revised ten-year prevalence rate of 3.15 per 100,000 population by applying the results from Castillo 2015 and Yin 2020 for six to ten-year survival rates in the pre-PBAC response.

4.14 The key changes in WM epidemiological assumptions are summarised in Table 7.

Table 7: Summary of WM incidence and prevalence rates

	March 2022			July 2024		
	per 100,000 population					
	Base case	Low	High	Base case	Low	High
Incidence rate	0.37	0.30	0.40	0.60	0.50	0.70
Prevalence rate	1.22	1.10	1.34	3.21	2.89	3.53

Source: Table 2.5, p11 of the submission, utilisation and cost model workbooks (original and updated submission), 'Sheet 8. ABS population'

Blue shading represents information previously considered by the PBAC.

4.15 The submission stated that the revised prevalence rate of 3.21 per 100,000 (updated to 3.15 per 100,000 in the pre-PBAC response) was higher than the previously estimated rate of 1.22 per 100,000, in line with an increase to the incidence by 62% compared to the March 2022 estimate. The submission claimed that the proposed ten-year time period is clinically plausible due to the indolent nature of the disease, such that patients who were diagnosed more than five years ago may be eligible for zanubrutinib treatment under the PBS. The submission provided a sensitivity analysis, varying the base case by plus or minus 10%, consistent with the sensitivity analysis in the March 2022 submission. There was no basis for the magnitude used in the sensitivity analyses.

Revised number of WM patients

4.16 The table below presents a comparison of the incident and prevalent WM population estimated in the March 2022 and July 2024 submissions. The assumption for the total Australian population remained unchanged from the March 2022 submission. For a direct comparison, Year 1 was still considered to be 2022.

Table 8: Comparison of incident and prevalent WM population

	Submission	Base case rate per 100,000	2022	2023	2024	2025	2026	2027
Population (million)	Both		26.73	27.15	27.56	27.97	28.37	28.77
Incident WM patients	March 2022	[redacted]	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1
	July 2024	[redacted]	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1
Five-year prevalent WM patients	March 2022	[redacted]	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1
Ten-year prevalent WM patients	July 2024	[redacted]	[redacted]2	[redacted]2	[redacted]2	[redacted]2	[redacted]2	[redacted]2

Source: Table 2.6, p11 of the submission, utilisation and cost model workbooks (original and updated submission), 'Sheet 8. ABS population'
Abbreviation: WM=Waldenström macroglobulinemia
Blue shading represents information previously considered by the PBAC.
The redacted values correspond to the following ranges:
[1] < 500
[2] 500 to < 5,000

4.17 An analysis of the PBS utilisation of zanubrutinib for WM (PBS item code 13041J) was undertaken by the DUSC Secretariat.

Table 9: Number of patients and prescriptions dispensed for zanubrutinib for WM

	2022-23	2023-24*
Incident (new) patients	[redacted]1	[redacted]1
Prevalent (all treated) patients	[redacted]1	[redacted]2
Number of prescriptions dispensed	[redacted]2	[redacted]2

Note: The PBS data was extracted based on the date of supply.
***** Data is part-year to 13 June 2024.
The redacted values correspond to the following ranges:
[1] < 500
[2] 500 to < 5,000

Revised number of WM patients treated with zanubrutinib

4.18 A summary of the estimated number of WM patients treated with zanubrutinib in the March 2022 and July 2024 submissions is provided in Table 10.

Table 10: Estimated WM patients eligible for treatment with zanubrutinib

	March 2022		July 2024	
	Method/Source	Value	Method/Source	Value
First line (1L) – incident patients				
Incident WM patients	AIHW 2017, Table 23, zanubrutinib PSD, March 2022	Yr 1: [redacted]1 Yr 2: [redacted]1 Yr 3: [redacted]1 Yr 4: [redacted]1 Yr 5: [redacted]1 Yr 6: [redacted]1	AIHW 2023a, Table 8	Yr 1: [redacted]1 Yr 2: [redacted]1 Yr 3: [redacted]1 Yr 4: [redacted]1 Yr 5: [redacted]1 Yr 6: [redacted]1
Eligible patients for 1L zanubrutinib	Estimated by applying the following PBS eligibility to the incident WM patient numbers: - % treated (70-80%) - sponsor's market research (increased over time) - % chemo-immunotherapy ineligible (30%) - sponsor's market research	Yr 1: [redacted]1 Yr 2: [redacted]1 Yr 3: [redacted]1 Yr 4: [redacted]1 Yr 5: [redacted]1 Yr 6: [redacted]1	No change	Yr 1: [redacted]1 Yr 2: [redacted]1 Yr 3: [redacted]1 Yr 4: [redacted]1 Yr 5: [redacted]1 Yr 6: [redacted]1

	March 2022		July 2024	
	Method/Source	**Value**	**Method/Source**	**Value**
Total 1L patients initiating zanubrutinib	Uptake to Year 3 (75-87%) - sponsor's market research (increase over time) Uptake for Years 4-6 (95%) -assumed patient preference for oral therapy	Yr 1: [redacted][1] Yr 2: [redacted][1] Yr 3: [redacted][1] Yr 4: [redacted][1] Yr 5: [redacted][1] Yr 6: [redacted][1]	No change	Yr 1: [redacted][1] Yr 2: [redacted][1] Yr 3: [redacted][1] Yr 4: [redacted][1] Yr 5: [redacted][1] Yr 6: [redacted][1]
Relapsed/refractory (2L+) – incident patients (Years 2-6)				
Incident WM patients diagnosed 2 years prior	Estimated using incident WM patients from two years prior to the year of interest from Year 2 onwards.	Yr 2: [redacted][1] Yr 3: [redacted][1] Yr 4: [redacted][1] Yr 5: [redacted][1] Yr 6: [redacted][1]	No change	Yr 2: [redacted][1] Yr 3: [redacted][1] Yr 4: [redacted][1] Yr 5: [redacted][1] Yr 6: [redacted][1]
Eligible patients for 2L zanubrutinib	Estimated by applying the following PBS eligibility to the incident WM patients diagnosed 2 years prior: - % treated (70-80%) - sponsor's market research - % progress to 2L (62%) - sponsor's market research - % survive to 2L (90%) - Castillo et al., 2015 - % BTKi naïve (80%) - sponsor's market research	Yr 2: [redacted][1] Yr 3: [redacted][1] Yr 4: [redacted][1] Yr 5: [redacted][1] Yr 6: [redacted][1]	Updated % survive to 2L (100%) - AIHW 2023a and Castillo et al., 2015	Yr 2: [redacted][1] Yr 3: [redacted][1] Yr 4: [redacted][1] Yr 5: [redacted][1] Yr 6: [redacted][1]
Total 2L+ patients initiating zanubrutinib from Year 2 onwards	Uptake to Year 2-3 (85%-87%) - sponsor's market research (increase over time) Uptake for Years 4-6 (95%) -assumed patient preference for oral therapy	Yr 2: [redacted][1] Yr 3: [redacted][1] Yr 4: [redacted][1] Yr 5: [redacted][1] Yr 6: [redacted][1]	No change	Yr 2: [redacted][1] Yr 3: [redacted][1] Yr 4: [redacted][1] Yr 5: [redacted][1] Yr 6: [redacted][1]
Relapsed/refractory (2L+) – prevalent patients (Year 1 only)				
Prevalent WM patients	Calculated by Australian population in 2020 x five-year prevalent rate of 1.22 per 100,000	[redacted][1]	Calculated by Australian population x ten-year prevalent rate of 3.21 per 100,000, Table 8	[redacted][2]
Eligible prevalent patients	Estimated by applying the following PBS eligibility to the prevalent WM patients in Year 1: - % treated (70%) - sponsor's market research - % progress to 2L (62%) - sponsor's market research - % survive to 2L (90%) - Castillo et al., 2015 - % BTKi naïve (80%) - sponsor's market research	[redacted][1]	Updated % survive to 2L (100%) - Castillo et al., 2015	[redacted][1]
GF patients	Estimated 100 patients to be enrolled in the early access program by 1 September 2022, assuming 100% uptake	[redacted][1]	No change	[redacted][1]
Eligible prevalent patients excl. GF	Calculated by eligible prevalent patient numbers less GF patients	[redacted][1]	Calculated by eligible prevalent patient numbers less GF patients, and then applied a 75% uptake rate	[redacted][1]

	March 2022		July 2024	
	Method/Source	**Value**	**Method/Source**	**Value**
Total WM patients initiating zanubrutinib	The sum of 1L and 2L+ patients, including GF patients.- estimated number of patients initiating zanubrutinib was revised in the March 2022 pre-PBAC response, accounting for 100 GF patients.	Yr 1: [redacted][1] Yr 2: [redacted][1] Yr 3: [redacted][1] Yr 4: [redacted][1] Yr 5: [redacted][1] Yr 6: [redacted][1]	The sum of 1L and 2L+ patients, including GF patients.	Yr 1: [redacted][1] Yr 2: [redacted][1] Yr 3: [redacted][1] Yr 4: [redacted][1] Yr 5: [redacted][1] Yr 6: [redacted][1]
Total WM patients receiving zanubrutinib	Estimated number of patients receiving zanubrutinib was revised in the pre-PBAC response, accounting for 100 GF patients and revised treatment durations (TN = 37.45 months, RR = 37.05 months).	**Yr 1:** [redacted][1] **Yr 2:** [redacted][1] **Yr 3:** [redacted][1] **Yr 4:** [redacted][1] **Yr 5:** [redacted][1] **Yr 6:** [redacted][1]	Calculated by incorporating the treatment duration and the number of patients treated per year (See paragraph 4.22).	**Yr 1:** [redacted][1] **Yr 2:** [redacted][1] **Yr 3:** [redacted][1] **Yr 4:** [redacted][1] **Yr 5:** [redacted][1] **Yr 6:** [redacted][1]

Source: compiled by the Secretariat during the evaluation; Tables 2.7, 2.8, 2.9 of the submission, utilisation and cost model workbooks (original and updated submission), 'Sheet 2a. Patients - incident', 'Sheet 2b. Patients, 'Sheet 2. Patients, and Table 1 of the March 2022 pre-PBAC response

Abbreviation:1L=first line treatment; 2L+=second line or later line treatment, BTKi=Bruton's tyrosine Kinase inhibitor, GF=grandfathered; R/R=relapsed/refractory; TN=treatment naïve

Note: the eligible second line incident patients in Year 1 were assumed to be included within the prevalent population.

Note: the sum of sub-totals may result in a different total due to rounding.

Blue shading represents information previously considered by the PBAC

The redacted values correspond to the following ranges:

[1] *< 500*

[2] *500 to < 5,000*

4.19 In this submission, the percentage of patients "survive to second line treatment" was revised from 90% to 100%, based on the submission's claim that the rate of progression to second line treatment has already factored in patient survival. That is, if a patient has advanced to second line treatment, it means that the patient has survived up to that point. Therefore, for the R/R population, the proportion of patients survive to second line treatment was proposed to be set at 100%.

4.20 The submission did not propose any changes to the parameters, except the percentage of patients that survive to second line treatment (see paragraph 4.19), that would impact the estimated number of patients receiving zanubrutinib. R/R patients initiating zanubrutinib were excluded from Year 1 as they were already accounted for in the prevalent or grandfathered population. While the March 2022 submission estimated that < 500 patients would receive zanubrutinib in Year 1 (< 500 first line and < 500 grandfathered), this has been updated to < 500 patients (Table 10). This increase is primarily driven by including < 500 patients from the revised prevalent population estimate.

4.21 The submission stated that the increase in the total number of patients initiating zanubrutinib from Year 2 onward (Table 10) is attributed to higher incidence rates in both the first line and second line treatment settings.

4.22 The total number of patients treated with zanubrutinib for WM was calculated by incorporating the following:

- Weighted average treatment duration of 37.21 months across all lines of treatment (initially estimated as [redacted] months but revised in the March 2022 pre-PBAC

response), based on 37.45 months for first line and 37.05 months for second line with the [redacted]-month financial stopping rule in place (paragraph 7.7, zanubrutinib, PSD, March 2022).

- Grandfathered patients were assumed to start treatment 6 months prior to the PBS listing of zanubrutinib, resulting in a shorter treatment duration of 31.21 months for this patient population.
- Patient numbers were projected to grow over the years to align with population growth trends, except for a decline in Year 4 as grandfathered patients are expected to discontinue treatment partway through Year 3, where a small number of prevalent patients would remain on treatment in Year 4 with their treatment duration of 37.05 months, which end in the second month of that year.

Estimated PBS usage and financial implications

4.23 The submission provided updated financial estimates (see Table 11) that were aligned with the revised estimated use of zanubrutinib for the treatment of WM. The financial impact to Services Australia will be determined by that agency as part of the post PBAC process.

4.24 The submission noted that there have been changes to pricing inputs to estimate the financial implications, but no changes to the assumptions since last considered by the PBAC in March 2022. The published approved ex-manufacturer price (AEMP) for zanubrutinib was reduced from $[redacted] to $[redacted], but the effective AEMP of $[redacted] was unchanged since its listing for WM on the PBS.

4.25 The submission presented financial estimates without any pricing changes to enable a direct comparison to the March 2022 submission. This allowed for isolating the impact of increased utilisation of zanubrutinib. The impact of the updated pricing inputs was considered minor compared to the financial estimates incorporating those new prices. Therefore, the financial estimates in the scenario without changes to pricing inputs were not included here, as they offered minimal additional insight.

Table 11: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients treated with zanubrutinib						
March 2022	[1]	[1]	[1]	[1]	[1]	[1]
July 2024	[1]	[1]	[1]	[1]	[1]	[1]
Number of zanubrutinib scripts dispensed (PBS/RPBS)[a]						
March 2022	[2]	[2]	[2]	[2]	[2]	[2]
July 2024	[2]	[2]	[2]	[2]	[2]	[2]
Estimated financial implications of zanubrutinib (cost to PBS/RPBS less co-payment)						
March 2022	[3]	[3]	[3]	[3]	[3]	[3]
July 2024	[4]	[4]	[4]	[4]	[4]	[4]
Estimated financial implications of currently listed treatments (cost to PBS/RPBS less co-payment)[b]						
March 2022	[5]	[5]	[5]	[5]	[5]	[5]
July 2024	[5]	[5]	[5]	[5]	[5]	[5]
Net financial implications						
March 2022	[3]	[3]	[3]	[3]	[3]	[3]
July 2024	[4]	[4]	[4]	[4]	[4]	[4]
Net financial impact from updated submission						
Net increase in value	[3]	[3]	[3]	[3]	[3]	[3]
% Net increase	%	%	%	%	%	%

Source: compiled by the Secretariat during the evaluation; Table 2.13, p17 of the submission, utilisation and cost model workbooks (original and updated submission), 'Sheet 3c. Impact – proposed (eff)', 'Sheet 4c. Impact - affected (eff)'

[a] Assuming number of scripts per year as estimated by the submission, Table 2.10 of the submission

[b] Based on the updated published DPMAs as of February 2024.for filgrastim (PBS item codes: 5742F, 6291D) $287.88, $307.77; cyclophosphamide (PBS item codes: 4327R, 7226H) $144.39, $188.46, and the same DPMQs for cyclophosphamide (1266P) $156.62; chlorambucil (1163F) $136.25, respectively, since last considered by the PBAC in March 2022.

Note: the patient co-payments were changed, with the General co-payment of $31.60 (reduced from $41.00) and the Concessional co-payment of $7.70 (increased from $6.60) as of February 2024.

Abbreviations: PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme.

Blue shading represents information previously considered by the PBAC

The redacted values correspond to the following ranges:

[1] *< 500*

[2] *500 to < 5,000*

[3] *$0 to < $10 million*

[4] *$10 million to < $20 million*

[5] *net cost saving*

4.26 The submission provided the revised financial estimates from 2022 (Year 1) and forward years, incorporating retrospective estimates for 2022-2023, including grandfathered patients. The evaluation noted that the approach to utilisation and financial estimates should be for the next six years.

4.27 It would be appropriate if the financial implications of listing zanubrutinib and its impact on currently listed medicines were estimated using revised parameters derived from the actual prescription volume data for zanubrutinib since its listing for the WM indication. While using the same PBS item statistics for bendamustine for indolent non-Hodgkin's lymphoma to estimate split prescription volume between public and private hospitals as proxy data would be acceptable, patient co-payments should have been derived from the distribution of patient categories using actual zanubrutinib PBS service data. The pre-PBAC response provided updated financial estimates (see Table 12), however, these updates were not based on the actual usage data for zanubrutinib.

4.28 The submission estimated that 500 to< 5,000 patients would be supplied zanubrutinib over the first six years of listing (< 500 in Year 1 to < 500 in Year 6), resulting in the net financial impact to the PBS/RPBS to be $70 million to < $80 million over six years (Year 1 $10 million to < $20 million to Year 6 $10 million to < $20 million).

4.29 The submission's revised utilisation of zanubrutinib proposed a substantial increase in the net financial impact to the PBS/RPBS over six years. While the previous estimate was $30 million to < $40 million, the net financial impact is expected to increase to $70 million to < $80 million over the same period in the revised model.

4.30 The pre-PBAC response proposed a decrease in the effective AEMP to $[redacted] to ensure the cost-effectiveness of zanubrutinib for WM in line with the requested reduction in the current subsidisation caps. The financial estimates were adjusted to account for changes in the prevalent population, effective price, and the timing of prevalent patients starting treatment (see Table 12 below).

Table 12: Revised estimated use and financial implications in the pre-PBAC response

Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use					
Number of patients treated with zanubrutinib					
1	*1*	*1*	*1*	*1*	*1*
Number of zanubrutinib scripts dispensed (PBS/RPBS)					
2	*2*	*2*	*2*	*2*	*2*
Estimated financial implications of zanubrutinib (cost to PBS/RPBS less co-payment)[a]					
3	*4*	*4*	*4*	*4*	*4*

Source: compiled by the Secretariat using Table 1 of the pre-PBAC response, utilisation and cost model workbook 'Sheet 3c. Impact – proposed (eff)', 'Sheet 4c. Impact - affected (eff)'

[a] Based on the proposed effective price for zanubrutinib of $[redacted]

Note: the patient co-payments were changed, with the General co-payment of $31.60 (reduced from $41.00) and the Concessional co-payment of $7.70 (increased from $6.60) as of February 2024.

Abbreviations: PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme; NP = not provided.

Italics in grey shading represent information provided in the pre-PBAC response but not evaluated.

The redacted values correspond to the following ranges:

1 < 500

2 500 to < 5,000

3 $0 to < $10 million

4 $10 million to < $20 million

4.31 As a Category 3 submission the financial estimates have not been independently evaluated.

Financial Management – Risk Sharing Arrangements

4.32 The submission stated that it is often challenging to quantify the epidemiology of rare diseases, such as WM, accurately due to a lack of comprehensive data. Given the limited data available, the sponsor relied on the best publicly accessible information to estimate the utilisation and financial implications for PBAC consideration in March 2022. However, recent data published by the AIHW demonstrated that the actual incidence and prevalence of WM was higher than previously estimated. This discrepancy was reflected in the actual utilisation of zanubrutinib in the first two years of listing, which exceeded the estimated levels (see Table 13). However, the evaluation considered that the submission did not sufficiently justify that the

proposed cap increases were solely attributable to a higher incidence and prevalence of WM than estimated, as other factors might also contribute to exceeding the subsidisation caps. The pre-PBAC response maintained that the higher-than-estimated incidence and prevalence are likely the key drivers of the higher utilisation of zanubrutinib observed since its listing.

4.33 The submission stated that the revised utilisation of $10 million to < $20 million in Year 2 is within 0.5% of the actual estimated utilisation of $[redacted] (Table 13). However, the estimated utilisation of $10 million to < $20 million was higher than the actual Commonwealth payment of $[redacted] in Year 1. The submission claimed that this discrepancy was attributed to the model's assumption that all prevalent patients would commence treatment with zanubrutinib on day 1 of Year 1.

Table 13: Summary of zanubrutinib RSA caps, Commonwealth payment vs updated financial impact

Year	Date range	Current RSA subsidisation Cap	Commonwealth payment[a]	Estimated utilisation[b]
1	July 2022 to June 2023	$[redacted]	$[redacted] (actual)	[redacted][1]
2	July 2023 to June 2024	$[redacted]	$[redacted] (estimate)	[redacted][1]

Source: Table 3.1, p18 of the submission

[a]. see Table *3* for more details

[b]. estimated financial implications of zanubrutinib = cost to PBS/RPBS less co-payment in Table 11.

The redacted values correspond to the following ranges:

[1] $10 million to < $20 million

4.34 The submission requested the subsidisation caps be amended from Year 3 of the current deed to align with the revised financial estimates.

4.35 As outlined in paragraph 2.8, the PBAC recognised the challenges of using an RSA to achieve cost-effectiveness as the estimated number of patients treated must be reached in order for the RSA to constrain the cost per patient. However, the PBAC considered, provided the expenditure caps were based on the average (not maximum) treatment durations from the economic models and the rebate for use above the expenditure caps was [redacted]%, that a cost-effective price would likely be achieved using an RSA (paragraph 7.6, zanubrutinib, PSD, March 2022). The PBAC previously considered that the listing of zanubrutinib would be cost-effective with an incremental cost-effectiveness ratio (ICER) of less than $45,000 to < $55,000 per quality-adjusted life year (QALY) gained for the R/R population and approximately $55,000 to < $75,000 per QALY for the TN population (paragraph 7.2, zanubrutinib, PSD, March 2022).

4.36 The pre-PBAC response argued that the actual number of patients to be treated with zanubrutinib will exceed the estimates in the later years of the deed, even after considering the requested increases to the utilisation estimates. The extrapolation of the ASPEN study, as reported in the March 2022 submission, suggested a treatment duration of over 7 years (i.e., 86.04 months), while the existing subsidisation caps were based on the average treatment duration at 37.21 months. Consequently, estimated utilisation is expected to diverge from actual utilisation starting in Year 3, as patients are likely to continue treatment for over 37.21 months. This discrepancy will result in actual utilisation increasing over time, while the estimated utilisation that is the basis

for the proposed caps will decline in Years 4 and 5 before increasing again with population growth.

5 PBAC Outcome

5.1 The PBAC provided advice regarding the subsidisation caps under the current risk sharing arrangement (RSA) for zanubrutinib (Brukinsa®) for the treatment of Waldenström macroglobulinemia (WM). The PBAC considered it was reasonable to make amendments to the financial estimates underpinning the RSA to reflect the proposed changes in incidence and prevalence based on new epidemiological data specific to the WM subset in Australia that had not been previously available. The PBAC was satisfied that the submission provided sufficient evidence to support the requested changes to the assumptions in terms of the incidence and prevalence in the March 2022 financial estimates that were the basis for the current RSA, and that although this represented a significant increase to the original estimates, the sponsor's proposed price reduction in the pre-PBAC response mitigated the financial impact in part.

5.2 The PBAC noted that the submission did not propose to change the basis for achieving cost-effectiveness through the RSA, which was intended to limit the treatment duration to a weighted average treatment duration of 37.21 months. The PBAC advised that the cost-effectiveness of zanubrutinib would remain acceptable if the subsidisation caps continue to be determined on the same basis, given that the requested changes affect only the number of patients and not the number of units per patient.

5.3 The PBAC noted that the utilisation of zanubrutinib for WM in the first two years of listing has been substantially higher than the March 2022 estimates (see Table 3). The PBAC considered an increase in the financial estimates, commensurate with the changes in incidence and prevalence, to be reasonable. In providing this advice, the PBAC indicated that the revised financial estimates are clearly higher, but the use of zanubrutinib would remain within the eligible population previously deemed cost-effective.

5.4 The PBAC acknowledged the clinical need for a targeted therapy for WM at the time of its recommendation in March 2022. The PBAC recalled that determining the appropriate incremental cost-effectiveness ratio (ICER) was difficult due to the indolent nature of the disease, making achieving cost-effectiveness challenging. The financial estimates were based on a treatment duration from the economic model that applied a financial stopping rule, and the RSA used to manage the total cost per patient. The PBAC noted that the previously recommended ICERs for the relapsed/refractory (R/R) and treatment-naïve (TN) populations were based on a weighted average treatment duration of 37.21 months, therefore, the effects of the RSA caps would not be seen until Year 3 or 4 of the deed. However, the actual utilisation of zanubrutinib over the first two years of its listing has significantly exceeded the previous estimates. The PBAC was of the view that, for this reason, the

previously recommended ICERs would remain acceptable with the increased subsidisation caps to achieve the cost-effectiveness of zanubrutinib.

5.5 The PBAC noted that the submission estimated 37% of asymptomatic patients would require treatment between 4 and 10 years after diagnosis (Maqbool 2020), impacting both the TN and R/R prevalence. As such, the previously used 5-year prevalence, which excluded patients diagnosed 5 years ago, was considered to be an inappropriate approach. With the representativeness of the US SEER data in the absence of Australian survival data beyond 5 years, the PBAC considered that the use of Castillo 2015 and Yin 2020 data to estimate the ten-year prevalence of WM in Australia was appropriate, noting that the survival rates from Australian and US data were comparable, as informed by the comparison across various studies in the pre-PBAC response.

5.6 The PBAC noted that it would have been beneficial for the sponsor to demonstrate how these epidemiological changes, especially incidence and prevalence, influence financial estimates independently of the impact of limiting the treatment duration. The PBAC indicated that similar patterns are expected for the increase in patient numbers, irrespective of lines of therapy, before and after applying the duration impact, however, the PBAC considered it had become more challenging to verify due to the modifications made in the pre-PBAC response.

5.7 The PBAC advised that, in addition to the epidemiological changes, the revised utilisation and financial estimates that underpin the increased subsidisation caps should be based on the appropriate inputs:

- reduced effective price for zanubrutinib; and
- current parameter values, especially patient co-payments to be derived from the prescription split between patient categories using actual zanubrutinib PBS service data (see paragraph 4.27).

5.8 The PBAC considered that, while the difficulty in determining the percentage increase in the RSA caps has been compounded by the modifications made in the pre-PBAC response, these estimates are likely to be lower than the proposed subsidisation caps outlined in the submission. The PBAC further advised that the RSA caps continue to reflect the average treatment duration of 37.21 months, aligning with the PBAC's initial intention of achieving cost-effectiveness, although this is not expected to be realised until Year 3 or 4 of the deed.

5.9 The PBAC noted that this submission is not eligible for an Independent Review because it received a positive recommendation.

Outcome:
Recommended

6 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

7 Sponsor's Comment

The Sponsor welcomes the PBAC's recommendation to amend the existing Risk Sharing Arrangement subsidisation caps of zanubrutinib for the treatment of Waldenström macroglobulinaemia, including the incorporation of new epidemiological data to future utilisation estimates.