6.01 ACALABRUTINIB, Tablet 100 mg, Calquence®, AstraZeneca Pty Ltd.

1 Purpose of submission

1.1 The Category 2 submission requested that the PBAC consider the sponsor's revised proposal for listing acalabrutinib for use in combination with bendamustine and rituximab (ABR) for patients with previously untreated Stage III or IV mantle cell lymphoma (MCL) who are ineligible for stem cell transplantation. This item was recommended at the July 2025 PBAC meeting.

1.2 Listing was requested on the basis of a cost-effectiveness analysis versus bendamustine and rituximab treatment alone. The key components of the resubmission are summarised in Table 1.

Table 1: Key components of the clinical issue addressed in the submission

Component	Description
Population	Patients with previously untreated Stage III or IV mantle cell lymphoma who are ineligible for ASCT.
Intervention	Induction (Cycles 1–6): acalabrutinib 100 mg orally twice daily for 6 cycles, bendamustine 90 mg/m^2 IV on Days 1 and 2 for 6 cycles, and rituximab 375 mg/m^2 on Day 1 for 6 cycles. Continuing therapy (Cycle 7 onwards): Patients achieving partial response or better after induction continue to receive acalabrutinib 100 mg orally twice daily, and up to 12 doses of rituximab 375 mg/m^2 once every 8 weeks, up to Cycle 30.
Comparator	Induction (Cycles 1–6): bendamustine 90 mg/m^2 IV on Days 1 and 2 for 6 cycles, and rituximab 375 mg/m^2 on Day 1 for 6 cycles. Continuing therapy (Cycle 7 onwards): Patients achieving partial response or better after induction receive up to 12 doses of rituximab 375 mg/m^2 once every 8 weeks, through no later than Cycle 30.
Outcomes	Progression free survival, overall response rate, overall survival, duration of response, time to response, patient reported outcomes, safety.
Clinical claim	In patients with previously untreated Stage III or IV mantle cell lymphoma, acalabrutinib in combination with bendamustine and rituximab is superior in terms of efficacy and inferior in terms of safety when compared to bendamustine and rituximab.

Source: Table 1-2, p5 of the submission.
ASCT = autologous stem cell transplant; IV = intravenous.
Notes: Cycle length is 28 days. Patients receive acalabrutinib/placebo until disease progression or unacceptable toxicity.
Blue shading represents information previously considered by the PBAC.

2 Background

Registration status

2.1 Acalabrutinib was registered by the Therapeutic Goods Administration (TGA) on 12 September 2025 for use in combination with bendamustine and rituximab for the

treatment of adult patients with previously untreated MCL who are not eligible for autologous haematopoietic stem cell transplantation.

Previous PBAC consideration

2.2 This is the second submission for acalabrutinib for the treatment of patients with previously untreated Stage III or IV MCL. At its July 2025 meeting, "the PBAC recommended ABR for the first line treatment of Stage III or IV MCL in patients who are ineligible for stem cell transplantation. The PBAC noted improvements in progression free survival (PFS) associated with acalabrutinib for this population. The PBAC considered the submission's economic model included some assumptions that were uncertain and overly optimistic. As such, the PBAC's recommendation was based on, among other matters, its assessment that the cost-effectiveness of acalabrutinib would be acceptable with a price reduction using a respecified economic model. The PBAC further advised that, as the cost-effectiveness of the first line listing relied on reduced use of Bruton tyrosine kinase inhibitors (BTKi) in the relapsed/refractory setting, a risk sharing arrangement (RSA) that accounts for reduced use of BTKi in relapsed/refractory (RR) MCL would be required" (paragraph 7.1, acalabrutinib Public Summary Document [PSD], July 2025 PBAC meeting).

2.3 The submission stated that the price implied by the PBAC's respecified base case was below the minimum price approved by their global office, thus the sponsor was unable to progress to listing. The main purpose for the submission was to request a revised effective price and revised RSA caps.

2.4 A summary of the key matters of concern raised by the PBAC at its July 2025 meeting and how the matters were addressed in the submission is presented in Table 2. This submission presented results from an updated analysis from ECHO (data cut-off date 15-Feb-25), which was used to inform the updated economic model.

Table 2: Summary of key matters of concern

Section	Matter of concern	How it was addressed in the submission
Acalabrutinib price	The PBAC noted a price reduction would be required to achieve the ICER between $55,000 to < $75,000 per QALY (using FAS without censoring for COVID-19) and $55,000 to < $75,000 per QALY (using the COVID-19 censored analysis) (paragraph 7.13, acalabrutinib PSD, July 2025 PBAC meeting).	Proposed effective EMP: $[redacted] (9% lower effective EMP than the July 2025 submission). However, the evaluation calculated that the EMP required for the parameters advised by the PBAC in July 2025 would be between $[redacted] (based on the FAS analysis) and $[redacted] (based on the COVID-19 censored analysis) using the RR BTKi prices known to the sponsor. Proposed effective DPMQ: $[redacted], based on 5% SPR from Apr 2026. DPMQ was updated to reflect July 2026 wholesaler mark-up changes for Section 85. This was used in the economic model.
Requested PBS restrictions	The PBAC recommended separate restrictions for induction and continuing treatment phases and a grandfathered restriction (paragraph 7.4, acalabrutinib PSD, July 2025 PBAC meeting).	Accepted separate restrictions for induction, continuing and grandfathered treatment phases.
Economic evaluation		
Time horizon in economic model	The economic model should be respecified using a 10-year time horizon (para 7.13, acalabrutinib PSD, July 2025 PBAC meeting) vs 20 years from the submission's base case.	Addressed. The submission applied a 10-year time horizon.
Subsequent therapy in economic model	BTKi costs should be included in the ABR arm consistent with ECHO (para 7.13, acalabrutinib PSD, July 2025 PBAC meeting).	Not addressed. The submission maintained the BTKi once per lifetime assumption for applying costs in the economic model, though the efficacy remained based on the trial data where subsequent BTKi use was permitted.
Financial estimates		
Treatment persistence	The PBAC noted persistence was applied in the economic model but not in the financial estimates (paragraph 7.15, acalabrutinib PSD, July 2025 PBAC meeting)	The submission's financial estimates were updated to include the acalabrutinib persistence population.
Risk Sharing Arrangement (RSA)	The PBAC expressed a preference for combined 1L and RR MCL caps as part of an RSA (paragraph 7.15, acalabrutinib PSD, July 2025 PBAC meeting).	The submission proposed a combined expenditure cap across 1L and RR MCL, including a "catch-up" adjustment for RR MCL over 2023–2027. The overall BTKi cap included RR MCL utilisation, proposed use of acalabrutinib in 1L MCL, and assumed offsets from reduced subsequent BTKi use, informed by the financial estimates analysis.

Source: Compiled during the evaluation based on Table 1.1 pp3-4.
ABR = acalabrutinib + bendamustine + rituximab; BTKi = Bruton tyrosine kinase inhibitor; MCL = mantle cell lymphoma; PBAC = Pharmaceutical Benefits Advisory Committee; PSD = public summary document; RR = relapse/refractory; RSA = risk sharing arrangement; 1L= first line treatment.

For more detail on PBAC's view, see section 5 PBAC outcome.

3 Requested listing

MEDICINAL PRODUCT medicinal product pack	Dispensed Price for Max. Qty	Max. qty packs	Max. qty units	№.of Rpts	Available brands
ACALABRUTINIB					
acalabrutinib 100 mg tablet, 56	$7,158.95 (published) $[redacted] (effective)	1	56	5	Calquence®

Requested restriction: induction treatment

Category / Program: General Schedule (Code GE)
Prescriber type: Medical Practitioners
Restriction type: Authority Required (telephone/online PBS Authorities system)
Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333. No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised.
Severity: Stage III or IV mantle cell lymphoma
Condition: Mantle cell lymphoma
Indication: Stage III or IV mantle cell lymphoma
Treatment Phase: First line therapy - Induction treatment
Clinical criteria:
The condition must be previously untreated
AND
Clinical criteria:
The treatment must be initiated in combination with rituximab
AND
Clinical criteria:
The condition must be symptomatic
AND
Clinical criteria:
Patient must not receive more than 6 cycles (12 doses) of treatment under this restriction
AND
Clinical criteria:
Patients must have a WHO performance status of 2 or less
AND
Clinical criteria:
Patient must not be eligible for stem cell transplantation

Source: Table 1-10 p26 of the submission

Requested restriction: continuing treatment

MEDICINAL PRODUCT medicinal product pack	Dispensed Price for Max. Qty	**Max. qty packs**	**Max. qty units**	**№.of Rpts**	**Available brands**
ACALABRUTINIB					
acalabrutinib 100 mg tablet, 56	$7,158.95 (published) $[redacted] (effective)	1	56	5	Calquence
Category / Program: General Schedule (Code GE)					
Prescriber type: I ☒Medical Practitioners					
Restriction type: ☒Authority Required (telephone/online PBS Authorities system)					
Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333. No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised.					
Severity: Stage III or IV mantle cell lymphoma					
Condition: Mantle cell lymphoma					
Indication: Stage III or IV mantle cell lymphoma					
Treatment Phase: First line therapy - Continuing treatment					
Clinical criteria:					
Patient must have previously received PBS-subsidised treatment with this drug for this indication					
AND					
Clinical criteria:					
Patient must not have developed disease progression while being treated with this drug for this indication					

Source: Table 1-11 p27 of the submission

Requested restriction: grandfather treatment

MEDICINAL PRODUCT medicinal product pack	Dispensed Price for Max. Qty	**Max. qty packs**	**Max. qty units**	**№.of Rpts**	**Available brands**
ACALABRUTINIB					
acalabrutinib 100 mg tablet, 56	$7,158.95 (published) $[redacted] (effective)	1	56	5	Calquence
Category / Program: General Schedule (Code GE)					
Prescriber type: Medical Practitioners					
Restriction type: Authority Required (telephone/online PBS Authorities system)					
Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333. No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised.					
Severity: Stage III or IV mantle cell lymphoma					
Condition: Mantle cell lymphoma					
Indication: Stage III or IV mantle cell lymphoma					
Treatment Phase: First line therapy - Grandfathering treatment – induction and maintenance					
Clinical criteria:					
Patient must have been receiving non-PBS subsidised treatment with this drug for this indication prior to [listing date]					
AND					
Clinical criteria:					
The treatment must have been initiated in combination with rituximab					
AND					
Clinical criteria:					
The treatment must have been initiated in combination with bendamustine					
AND					
Clinical criteria:					
The condition must have been symptomatic prior to being treated with this drug for this indication					
AND					
Clinical criteria:					
Patient must have had a WHO performance status of 2 or less prior to being treated with this drug for this indication					
AND					
Clinical criteria:					
Patient must not have been eligible for stem cell transplantation at the time of commencement of this therapy for this indication					
AND					
Clinical criteria:					
Patient must not have developed disease progression while being treated with this drug for this indication					
AND					
Clinical criteria:					
Patient must not receive more than 6 cycles (12 doses) of PBS and non-PBS subsidised treatment with this drug as induction therapy					
OR					
Patient must have previously received up to a maximum of 6 cycles (12 doses) of this drug as induction therapy					

Source: Table 1-12 pp27-28 of the submission

3.1 Flow on changes to the PBS restrictions for bendamustine (PBS item codes 10760H and 10763L) were also presented.

Requested restriction: flow on changes to bendamustine PBS restrictions

MEDICINAL PRODUCT Form	**PBS item code**	**Max. Amount**	**№.of Rpts**
BENDAMUSTINE HYDROCHLORIDE Injection	$208.19 (Public) $255.46 (Private)	200 mg	11
Category / Program: GENERAL - General Schedule (Code GE)			
Prescriber type: Medical Practitioners			
Restriction type: Authority Required (STREAMLINED)			
Administrative Advice: No increase in the maximum number of repeats may be authorised.			
Indication: Previously untreated stage III or IV mantle cell lymphoma			
Treatment Phase: Induction treatment			
Clinical criteria:			
The condition must be CD20 positive			
AND			
Clinical criteria:			
The condition must be previously untreated			
AND			
Clinical criteria:			
The treatment must be in combination with rituximab,			
OR			
The treatment must be in combination with rituximab and acalabrutinib			
AND			
Clinical criteria:			
The condition must be symptomatic			
AND			
Clinical criteria:			
The treatment must be for induction treatment purposes only			
AND			
Clinical criteria:			
Patient must not receive more than 6 cycles (12 doses) of treatment under this restriction			
AND			
Clinical criteria:			
Patient must not be eligible for stem cell transplantation			

Source: Table 1-13 p30 of the submission

3.2 The submission proposed separate restrictions for induction, continuing treatment, and for grandfathered patients, which was unchanged from that recommended by the PBAC at its July 2025 meeting. At that time, the PBAC concluded it would be appropriate to permit continuation of acalabrutinib if bendamustine and/or rituximab are ceased due to intolerance, and that it was reasonable to restrict BTKi listings to once in a lifetime (paragraph 7.4, acalabrutinib PSD, July 2025 PBAC meeting).

3.3 The submission's proposed effective price was [redacted]% lower than that proposed in the July 2025 submission. The proposed effective EMP ($[redacted]) was consistent with acalabrutinib in first line chronic lymphocytic leukaemia and small lymphocytic leukaemia at the time of submission (i.e. prior to the 1 April 2026 anniversary price reduction to $[redacted]), and lower than the effective EMP in RR MCL ($[redacted]). As noted in paragraph 4.33, a proportion of Commonwealth expenditure is intended to be rebated through the RSA in order to achieve a cost-effective price.

3.4 The requested population was unchanged from the July 2025 submission, with acalabrutinib restricted to once-in-a-lifetime use. Therefore, patients treated with acalabrutinib in the first-line setting would not be eligible to receive a BTKi in the RR setting. This was consistent with the Economics Sub-Committee's (ESC) previous advice that a once-in-a-lifetime restriction would be reasonable given the lack of evidence supporting benefit with repeated BTKi use (paragraph 3.5, acalabrutinib PSD, July 2025 PBAC meeting). However, the key trial, ECHO, permitted subsequent BTKi use post-progression.

3.5 The submission stated that a patient access program for acalabrutinib in patients with previously untreated MCL commenced in September 2025, upon TGA registration. As of March 2026, approximately < 500 patients had commenced treatment. The submission estimated < 500 patients would be on treatment at the time of PBS listing (and potentially eligible for access to treatment via the proposed grandfather restriction).

For more detail on PBAC's view, see section 5 PBAC outcome.

4 Consideration of the evidence

Sponsor hearing

4.1 There was no hearing for this item.

Consumer inputs

4.2 The PBAC noted and welcomed the input from three organisations via the Office of Health Technology Assessment Consultation Hub. The Australasian Leukaemia and Lymphoma Group (ALLG) and Haematology Society of Australia and New Zealand (HSANZ) highlighted the unmet need in transplant ineligible MCL patients, especially those who are older, those with high-risk disease features and those in whom fitness

at relapse cannot be assumed. The input emphasised the heterogeneous nature of this patient population.

4.3 The input outlined the clinical importance of delaying disease progression in the older transplant-ineligible population, noting the burden of relapse and disease-related hospitalisations on functional independence and quality of life. The organisations noted the improvements in PFS observed in the updated trial data, while acknowledging that a statistically significant improvement in OS has not been demonstrated to-date.

4.4 The input outlined that the choice between 1L ABR versus subsequent BTKi therapy in the RR setting should be individualised based on clinical judgement.

4.5 Lymphoma Australia outlined the value of prolonging PFS to patients, including preserving quality of life, reducing the disruption associated with ongoing disease management, and delaying the emotional impact of relapse. Lymphoma Australia noted that the benefits are also seen in high-risk groups.

Clinical trials

4.6 The key clinical evidence was unchanged from that presented in the July 2025 submission. The key head-to-head trial (ECHO) compared ABR to placebo with bendamustine and rituximab in patients with previously untreated MCL.

4.7 The results presented in the July 2025 submission were from an interim analysis with a data cut-off of 15 February 2024. Longer-term data from ECHO (data cut-off: 15-Feb-2025) is new in this submission.

4.8 Details of the trials presented in the submission are provided in Table 3.

Table 3: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
ECHO	A phase 3, randomised, double-blind, placebo-controlled, multicenter study of bendamustine and rituximab (BR) alone versus in combination with acalabrutinib (ACP-196) in subjects with previously untreated mantle cell lymphoma (ECHO; ACE-LY308 / NCT02972840).	Clinical Study Report – Interim Analysis based on data-cut of 15 February 2024
	A Phase 3, Randomised, Double-blind, Placebo-controlled, Multi-center Study BR Alone Versus in Combination with Acalabrutinib (ACEP-196) in Subjects with Previously Untreated Mantle Cell Lymphoma (ECHO)	Clinical Study Report updated analysis based on data-cut of 15 February 2025 (Tables and Figures only)
	Wang M, Salek D, Belada D, Song Y, Jurczak W, Kahl BS, Paludo J, Chu MP, Kryachok I, Fogliatto L, Cheah CY, Morawska M, Sancho JM, Li Y, Patti C, Forsyth C, Zhang J, Lesley R, Ramadan S, Rule S, Dreyling M; ECHO investigators; ECHO Investigators. Acalabrutinib Plus Bendamustine-Rituximab in Untreated Mantle Cell Lymphoma.	J Clin Oncol. 2025 Jul 10;43(20):2276-2284. doi: 10.1200/JCO-25-00690.
	Wang M, et al. A phase 3 study of acalabrutinib plus bendamustine and rituximab in elderly (aged ≥65 years) treatment-naïve patients with mantle cell lymphoma.	Hematol Oncol 2019; 37: 554-555. (conference abstract)
	Wang M, Paludo J, de Holanda Farias JS, Villa D, Forsyth C, John E, Che M, Arora H, Delury C, Otero V, Song Y. Time to third-line treatment after bendamustine-rituximab with or without acalabrutinib in patients with previously untreated mantle cell lymphoma: Updated analysis of the phase 3 ECHO trial after 50 months of follow-up.	Blood. 2025 Nov 3; 146:885. (conference abstract)
	Wang M, Paludo J, de Holanda Farias JS, Villa D, Forsyth C, John E, Che M, Arora H, Delury C, Otero V, Song Y. Time to third-line treatment after bendamustine-rituximab with or without acalabrutinib in patients with previously untreated mantle cell lymphoma: Updated analysis of the phase 3 ECHO trial after 50 months of follow-up.	Blood. 2025 Nov 3;146:885. Conference Presentation
	Wang M.L., Spurgeon S., Pavlovsky M., Cheah C.Y., Villa D., Luminari S., Otero V., De Jesus G., Lesley R., Zinzani P.L. (2025). MINIMAL RESIDUAL DISEASE with BENDAMUSTINE-RITUXIMAB with or WITHOUT ACALABRUTINIB in PATIENTS with PREVIOUSLY UNTREATED MANTLE CELL LYMPHOMA: RESULTS from the PHASE 3 ECHO TRIAL.	30th Congress of the European Hematology Association Annual Congress, EHA2025. HemaSphere. http://dx.doi.org/10.1002/hem3.70152 (conference abstract)
	Dreyling M., Zinzani P.L., Pavlovsky M.A., Bouabdallah K., Bastos-Oreiro M., John E., Otero V., Goy A.H. (2025). MCL-725: Efficacy of Rituximab-Bendamustine With or Without Acalabrutinib in Patients With Untreated, High-Risk Mantle Cell Lymphoma: An Analysis of the Phase 3 ECHO Trial,	Society of Hematologic Oncology Thirteenth Annual Meeting. Clinical Lymphoma, Myeloma and Leukemia. http://dx.doi.org/10.1016/S2152-2650(25)02476-0 (conference abstract)
	Dreyling M., Zinzani P.L., Pavlovsky M.A., Bouabdallah K., Bastos-Oreiro M., John E., Otero V., Goy A.H. (2025). EFFICACY OF RITUXIMAB-BENDAMUSTINE WITH OR WITHOUT ACALABRUTINIB IN PATIENTS WITH UNTREATED, HIGH-RISK MANTLE CELL LYMPHOMA: AN ANALYSIS OF THE PHASE 3 ECHO TRIAL.	30th Congress of the European Hematology Association Annual Congress, EHA2025. HemaSphere. http://dx.doi.org/10.1002/hem3.70151 (conference abstract)

Source: Table 2-5, p43 of the submission.
The full text trial publication of ECHO by Wang et al (2025) was identified by the submission's literature search but not included in Table 2-5 p43 of the submission.
Blue shading represents information previously considered by the PBAC.

4.9 The key features of ECHO are summarised in Table 4.

Table 4: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
ECHO	598	Randomised, placebo-controlled, double blind, multicentre trial. 5.52 months induction followed by maintenance until disease progression	Low [a]	Patients aged ≥65 with previously untreated mantle cell lymphoma, ECOG status ≤2	PFS, OS, best ORR, duration of response, time to response, EQ-5D-5L, safety	PFS, OS, time on treatment, time to first subsequent therapy, use of subsequent treatments, EQ-5D-5L, adverse events

Source: Section 2.3, pp33-38 of the July 2025 submission.
ECOG = European Cooperative Oncology Group; ORR = overall response rate; OS = overall survival; PFS = progression-free survival.
[a] The previous evaluation (July 2025) considered that the risk of bias for ECHO was low to unclear due to the exclusion of patients from the China cohort (n=37) from the full analysis set.
Blue shading represents information previously considered by the PBAC.

4.10 ECHO was a well-designed, multi-national, randomised controlled trial (paragraph 7.7, 6.01 acalabrutinib PSD July 2025). ECHO is currently ongoing and is expected to be completed by 15 February 2027.[1]

Comparative effectiveness

4.11 The submission presented an updated analysis for the data cut-off of 15-Feb-25 (an additional year of follow-up). The median time on study was 51.9 months.

Progression Free Survival

4.12 Results for PFS in ECHO are summarised in Table 5, with Kaplan-Meier curves for the full analysis set (FAS) in Figure 1. Results from the updated analysis (data cut-off, 15-Feb-25) were consistent with the interim analysis (data cut-off 15-Feb-24). Censoring in the FAS was 58.7% at the 15-Feb-24 data cut-off and 57.5% at the 15-Feb-25 data cut-off.

[1] URL: https://clinicaltrials.gov/study/NCT02972840#publications

Table 5: PFS by IRC assessment, FAS excluding and including censoring for COVID-19 related deaths

	Interim analysis (Data cut-off 15-Feb 24)				Updated analysis (Data cut-off 15-Feb 25)			
	Full analysis set		COVID-19 analysis [a]		Full analysis set		COVID-19 analysis [a]	
	ABR (N = 299)	PBR (N = 299)	ABR (N = 299)	PBR (N = 299)	ABR (N = 299)	PBR (N = 299)	ABR (N = 299)	PBR (N = 299)
Median follow up, months (range)	46.1 (0.03, 80.1)	44.4 (0.03, 81.3)	NR	NR	53.0 (0.03, 92.4)	50.8 (0.03, 93.0)	NR	NR
Events, n (%)	110 (36.8)	137 (45.8)	83 (27.8)	117 (39.1)	111 (37.1)	143 (47.8)	84 (28.1)	123 (41.1)
Death	53 (17.7)	38 (12.7)	26 (8.7)	18 (6.0)	54 (18.1)	40 (13.4)	27 (9.0)	20 (6.7)
Disease progression	57 (19.1)	99 (33.1)	57 (19.1)	99 (33.1)	57 (19.1)	103 (34.4)	57 (19.1)	103 (34.4)
Censored	189 (63.2)	162 (54.2)	216 (72.2)	182 (60.9)	188 (62.9)	156 (52.2)	215 (71.9)	176 (58.9)
PFS (months), median (95% CI)	66.4 (55.1, NE)	49.6 (36.0, 64.1)	NE (66.4, NE)	61.6 (49.6, 68.9)	71.8 (60.2, NE)	47.8 (36.1, 61.6)	NE (71.8, NE)	60.8 (47.8, 68.9)
HR (95% CI), stratified analysis	**0.73 (0.57, 0.94) 0.0160**		**0.64 (0.48, 0.84) 0.0017**		**0.69 (0.53, 0.88) 0.003**		**0.59 (0.45, 0.78) 0.0002**	
Kaplan-Meier estimates of PFS probability by timepoint (%)								
24 months (95% CI)	76.7 (71.1, 81.3)	66.2 (60.1, 71.6)	80.3 (74.9, 84.6)	69.2 (63.2, 74.4)	76.7 (71.1, 81.4)	66.3 (60.3, 71.7)	80.3 (75.0, 84.6)	69.3 (63.3, 74.5)
36 months (95% CI)	64.5 (58.1, 70.2)	56.1 (49.7, 62.0)	74.0 (68.0, 79.0)	62.1 (55.7, 67.8)	64.9 (58.6, 70.5)	56.5 (50.1, 62.3)	74.2 (68.3, 79.2)	62.4 (56.0, 68.1)
48 months (95% CI)	59.5 (52.8, 65.5)	50.4 (43.8, 56.6)	69.9 (63.5, 75.4)	57.3 (50.5, 63.5)	60.6 (54.1, 66.5)	49.8 (43.3, 55.9)	70.9 (64.6, 76.3)	56.4 (49.7, 62.5)

Source: Table 2-17, p56 of the July 2025 submission; Table 14.1.1.3, ECHO clinical study report tables and figures' Table 2-20 pp70-71 of the submission; Table 14.2.1 p273, Table 14.2.1.4 p281, ECHO CSR; Table 14.1.1.1 p72, Table14.2.1 p87, Table 1.1 p7 data-cut-off 15 Feb 2025.

ABR = acalabrutinib + bendamustine + rituximab; CI = confidence interval; FAS = full analysis set; HR = hazard ratio; IRC = Independent Review Committee; NE = not estimable; PBR = placebo + bendamustine + rituximab; PFS = progression free survival.

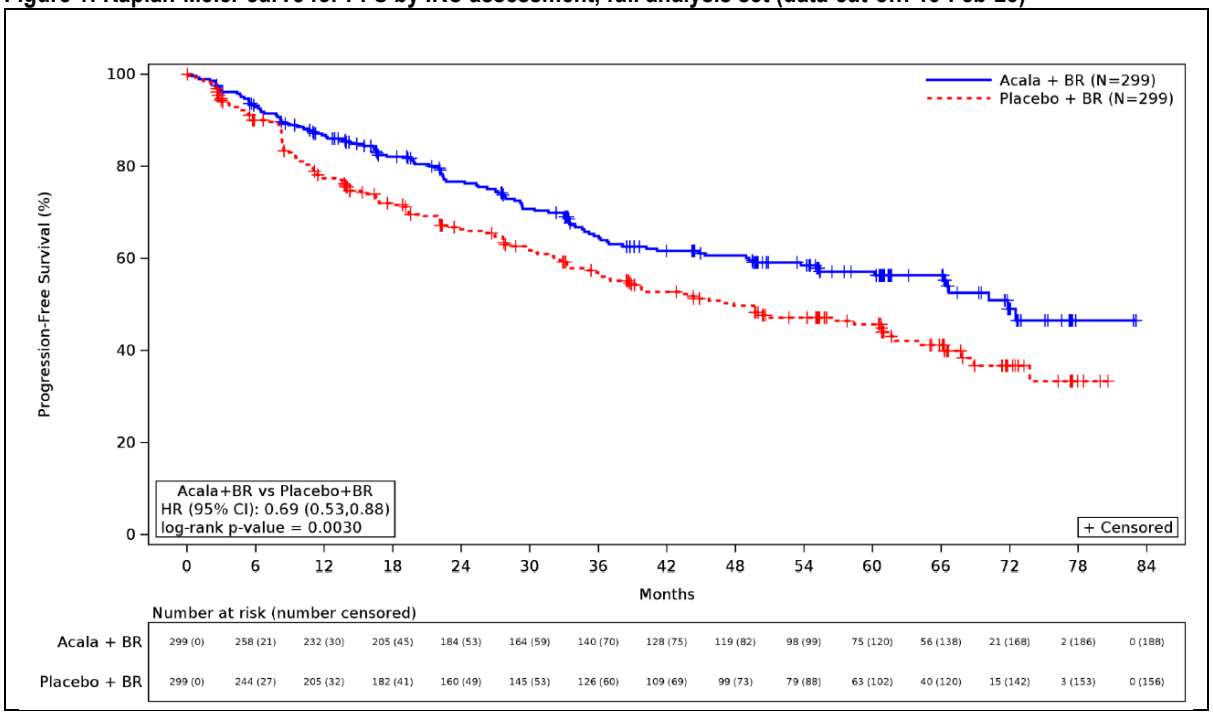
Bold indicates statistically significant results.

[a] Excluding patients with death related to COVID-19 and without progressive disease prior to death.

Notes: Stratified by randomisation stratification factors: geographic region (North America, Western Europe, Other) and simplified MIPI score (low risk [0 to 3], intermediate risk [4 to 5], high risk [6 to 11]).

Blue shading represents information previously considered by the PBAC.

Figure 1: Kaplan-Meier curve for PFS by IRC assessment, full analysis set (data cut-off: 15-Feb-25)



Source: Figure 2-8, p73 of the submission
Abbreviations: Acala, acalabrutinib; BR, bendamustine + rituximab; CI, confidence interval; HR, hazard ratio; IRC, Independent Review Committee; PFS = progression free survival

Overall survival

4.13 Results for OS in ECHO are summarised in Table 6, with Kaplan-Meier curves for the FAS in Figure 2. The OS data for ECHO remained relatively immature, with only 36%-39% (FAS) of patients having experienced an event (i.e., death) in the updated data cut-off. Censoring in the FAS was 66.1% in the previous data cut-off and 62.5% in the updated data cut-off. Results from the updated data (15-Feb-25) were consistent with the interim analysis (15-Feb-24).

Table 6: OS by IRC assessment, FAS and censoring for COVID-19 related deaths

	Interim analysis (Data cut-off 15-Feb 24)				Updated analysis (Data cut-off 15-Feb 25)			
	Full analysis set		COVID-19 analysis [a]		Full analysis set		COVID-19 analysis	
	ABR (N = 299)	PBR (N = 299)	ABR (N = 299)	PBR (N = 299)	ABR (N = 299)	PBR (N = 299)	ABR (N = 299)	PBR (N = 299)
Median follow up, months (range)	46.1 (0.03, 80.1)	44.4 (0.03, 81.3)	NR		51.9 (0.03, 93.0)		51.9 (0.03, 93.0)	
Events, n (%)	97 (32.4)	106 (35.5)	64 (21.4)	80 (26.8)	108 (36.1)	116 (38.8)	75 (25.1)	90 (30.1)
Death (all-cause)	97 (32.4)	106 (35.5)	64 (21.4)	80 (26.8)	108 (36.1)	116 (38.8)	75 (25.1)	90 (30.1)
Deaths from COVID-19	NA	NA	33 (11.0)	26 (8.7)	NA	NA	33 (11.1)[b]	26 (8.8)[b]
Censored	202 (67.6)	193 (64.5)	235 (78.6)	219 (73.2)	191 (63.9)	183 (61.2)	NR	NR
OS (months), median (95% CI)	NE (72.1, NE)	NE (73.8, NE)	NE (NE, NE)	NE (73.8, NE)	NE (73.3, NE)	NE (73.8, NE)	NE (NE, NE)[c]	NE (85.0, NE)[c]
HR (95% CI), stratified analysis	0.86 (0.65, 1.13)		0.75 (0.53, 1.04)		0.87 (0.67, 1.13)		0.78 (0.57, 1.06)[c]	
Kaplan-Meier estimates of OS by timepoint (%)								
24 months (95% CI)	83.8 (79.0, 87.6)	79.1 (73.9, 83.4)	87.0 (82.5, 90.4)	82.8 (77.8, 86.8)	83.8 (79.0, 87.6)	78.8 (73.6, 83.2)	NR	NR
36 months (95% CI)	73.8 (68.2, 78.7)	68.8 (62.9, 73.9)	83.0 (78.0, 87.0)	75.5 (69.8, 80.2)	73.8 (68.1, 78.5)	68.3 (62.5, 73.5)	NR	NR
48 months (95% CI)	68.0 (62.0, 73.3)	64.3 (58.2, 69.7)	78.8 (73.2, 83.3)	72.7 (66.8, 77.7)	68.3 (62.3, 73.4)	63.3 (57.2, 68.7)	NR	NR

Source: Table 2-18, p57 of the July 2025 submission; Table 2-21 p74, Table 2-22 p76 of the submission; Table 14.2.5.1 pp93-94, data-cut-off 15 Feb 2025; Submission attachment 3.2, file echo_iemt0160_itt_os_c19.docx.

ABR = acalabrutinib + bendamustine + rituximab; CI = confidence interval; FAS = full analysis set; HR = hazard ratio; IRC = Independent Review Committee; NE = not estimable; NR = not reported; OS = overall survival; PBR = placebo + bendamustine + rituximab.

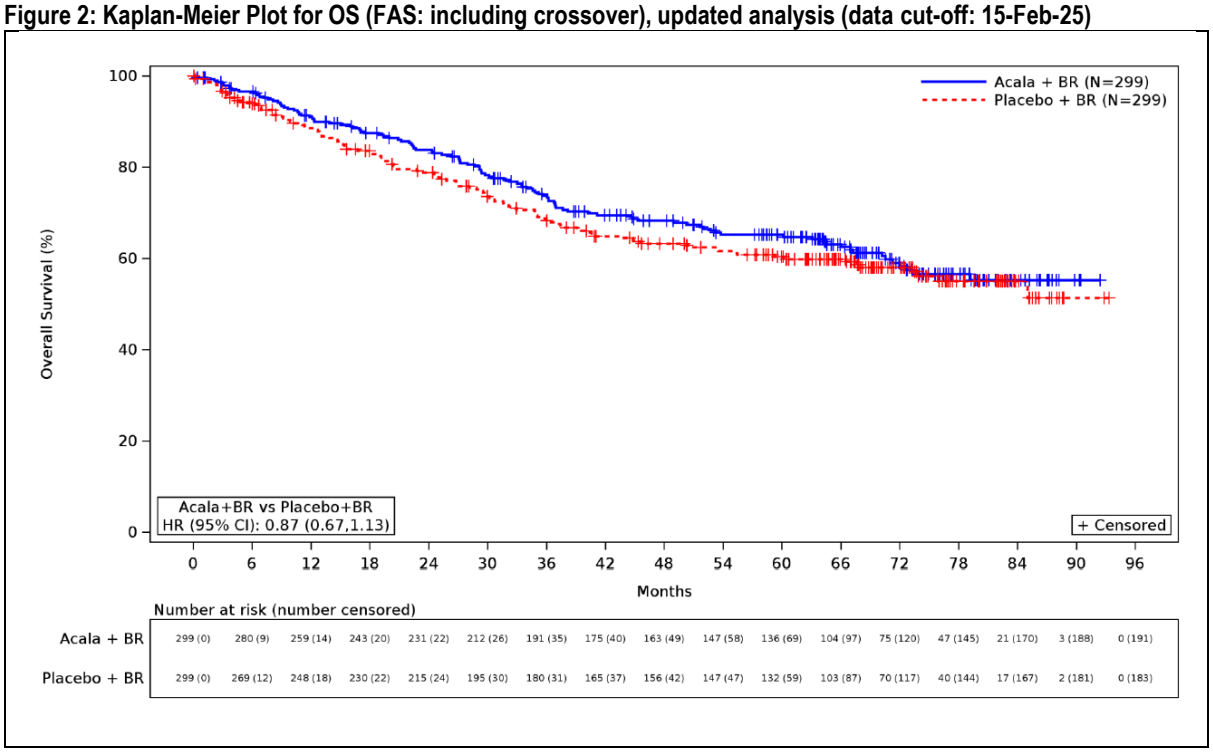
[a] Censoring COVID-19 deaths include all grade 5 Confirmed/Suspected COVID-19 infection adverse events and deaths due to a reason specified as COVID-19.

[b] Figures could not be validated during the evaluation.

[c] Figures validated during the evaluation were not consistent with sources for data presented in Table 2-22 p76 of the submission which were from a PowerPoint presentation (dated the 12-Aug-2025) for the 67th American Society of Hematology Annual Meeting.

Blue shading represents information previously considered by the PBAC.

Figure 2: Kaplan-Meier Plot for OS (FAS: including crossover), updated analysis (data cut-off: 15-Feb-25)



Source: Figure 2-11 p76 of the submission; ECHO Feb-25 DCO CSR Tables and Figures; Figure 14.2.5.2
Acala + BR= acalabrutinib + bendamustine + rituximab; CI = confidence interval; FAS = full analysis set; IRC = Independent Review Committee; Placebo + BR, placebo + bendamustine + rituximab; OS = overall survival

Comparative harms

4.14 The submission presented an updated safety analysis using the updated data cut-off (15-Feb-25). A small number of additional serious treatment emergent adverse events (TEAEs) and grade 3 or higher TEAEs were observed in the updated data (consistent with longer follow-up); however, the overall safety profile remained largely consistent with the earlier data.

Clinical claim

4.15 The clinical claim was unchanged in this submission, with ABR described as superior in terms of effectiveness and inferior in terms of safety compared with placebo in combination with BR. The PBAC previously considered these claims were reasonable and supported by the evidence (paragraph 6.29 and 6.30, 6.01 acalabrutinib PSD July 2025). Given the consistency between the evidence presented in the July 2025 submission and this submission, the evaluation and the ESC considered these claims remained reasonable.

4.16 The PBAC considered that the claim of superior comparative effectiveness was reasonable, supported by the data for the primary outcome (i.e. progression free survival).

4.17 The PBAC considered that the claim of inferior comparative safety was reasonable.

Economic analysis

4.18 The submission presented a stepped economic evaluation of ABR versus PBR in patients with previously untreated stage III or IV MCL. The economic evaluation was based on the results of ECHO using the COVID-19 censored analysis, with additional modelled data. Similar to the previous submission, the current submission presented limited information using the FAS results (i.e. without censoring for COVID-19), however modelled results using the FAS are presented herein.

4.19 The PBAC previously noted that the July 2025 submission's economic model included some assumptions that were uncertain and overly optimistic (paragraph 7.1, acalabrutinib minutes, July 2025 PBAC meeting), and advised that the economic model should be respecified as follows:

- a 10-year time horizon; and
- include BTKi costs in the ABR arm consistent with ECHO (paragraph 7.13, acalabrutinib PSD, July 2025 PBAC meeting); and
- the cost-effectiveness of acalabrutinib would be acceptable with a price reduction to achieve an incremental cost effectiveness ratio (ICER) between $55,000 to < $75,000 per quality adjusted life year (QALY) (using the FAS without censoring for COVID-19) and $55,000 to < $75,000 per QALY (using the COVID-19 censored analysis) (paragraph 7.13, acalabrutinib minutes, July 2025 PBAC meeting).

4.20 In response, the submission adopted a 10-year time horizon (versus 20-year in its July 2025 base case) as advised by the PBAC. However, the submission did not include BTKi costs in the ABR arm arguing that, in Australian clinical practice, patients would not receive subsequent BTKi therapy (following first-line acalabrutinib) given the proposed PBS restriction includes a once per lifetime rule for BTKi therapy. However, the pre-PBAC response provided revised economic model scenarios that included subsequent BTKi costs in the ABR arm (refer to Table 11).

4.21 In addition, key inputs for the economic model were updated as follows:

- clinical data were updated based on the February 2025 data cut-off (until median follow-up of 52 months);
- subsequent treatment data with further downstream lines of treatment were also updated to be based on the February 2025 data cut-off; and
- the acalabrutinib EMP was revised to $[redacted]. During the evaluation it was estimated that the EMP that would be required for the parameters advised by the PBAC in July 2025 would be between $[redacted] (based on the FAS analysis) and $[redacted] (based on the COVID-19 censored analysis).

4.22 A summary of the key components of the economic model is presented Table 7.

Table 7: Summary of model structure, key inputs and rationale (as presented in the submission)

Component	Description
Type of analysis	Cost-effectiveness analysis and cost-utility analysis
Treatments	Acalabrutinib with bendamustine and rituximab versus placebo with bendamustine and rituximab
Outcomes	Progression free life years; life years; quality-adjusted life years
Time horizon	10 years
Cycle length	28 days
Methods used to generate results	Partitioned survival analysis
Health states	Progression free; progressed disease; dead
Allocation to health states	The proportions of patients who were progression free, progressed and dead were informed by modelled overall survival (OS) and progression free survival (PFS) curves. PFS was further partitioned into on- and off-treatment using time on treatment (TOT) curves. Kaplan-Meier estimates for OS, PFS and TOT, censored for COVID-19 related deaths in the model base case, were derived from ECHO and were used directly in the model up to 52 months (based on the median duration of follow up, noting this timepoint was revised in some of the pre-PBAC response's revised economic model scenarios), then extrapolated using standard parametric functions. OS, PFS and TOT were adjusted to ensure that the risks of death, disease progression, and treatment discontinuation were not lower than the risk of general population mortality in any cycle, based on Australian life tables (ABS, Life expectancy, 2021-2023 (released 11 November 2025)).
Utility values	The utility associated with the progression free health state (0.830) was based on EQ-5D-5L data from ECHO, cross-walked to EQ-5D-3L (UK value set) based on descriptive summary statistics for pre-progression patients in the placebo arm. Limited utility data were available for patients following disease progression in ECHO. The utility associated with the progressed disease health state (0.759) was based on the utility decrement associated with progressed disease derived from the LYM-3002 trial (reported in the van Keep 2016 economic evaluation). The difference between the pre-progression and post-progression utilities of 0.071 was subtracted from the progression free health state utility of 0.830 derived from ECHO. Adverse event disutilities were based on the incidence of grade 3 or higher adverse events in ECHO, and selected published utility estimates from a catalogue of EQ-5D index scores based on UK preferences applied to responses to the EQ-5D questionnaire in the US-based Medical Expenditure Panel Survey (Sullivan 2011). The average adverse event disutility per patient per cycle was derived assuming patients were at risk of adverse events over 60 months.
Costs	The costs of first line treatment regimens were based on the dosage regimens in ECHO, the proposed effective DPMQ of acalabrutinib and weighted DPMAs for bendamustine and rituximab, the relative dose intensity for acalabrutinib in ECHO and the assumption of perfect adherence for bendamustine and rituximab, and treatment persistence informed by extrapolated time on treatment curves from ECHO. The proportions of patients receiving subsequent anti-cancer treatment were informed by extrapolated time to first subsequent treatment curves from ECHO. The distribution of use of first subsequent therapies was informed by use of chemotherapies and BTKi as subsequent anti-cancer therapies in ECHO (first to third subsequent line after failing ABR or PBR), and the assumption that patients who received acalabrutinib in the first line setting would not be eligible for subsequent treatment with a BTKi (this assumption was amended in the pre-PBAC response's revised economic model scenarios). Subsequent chemotherapy costs were based on alternating R-CHOP and R-DHAP dosing schedules in eviQ, weighted DPMAs, and an average duration of treatment of 3.7 months, based on the median duration of R-CHOP treatment reported in the LYM-3002 trial included in the November 2015 ibrutinib submission. Subsequent BTKi costs were based on the recommended dosage regimen of acalabrutinib for RR MCL in the acalabrutinib product information, the effective DPMQ for acalabrutinib for RR MCL, and an average duration of treatment of 17.8 months, based on the median duration of zanubrutinib treatment reported in one of 2 studies included in the July 2021 zanubrutinib submission (Study 206) noting this duration was revised in some of the pre-PBAC response's revised economic model scenarios. Chemotherapy administration costs were based on the MBS item fee.

Component	Description
	Health state costs were based on the initial phase costs over 12 months associated with non-Hodgkin lymphoma derived from Goldsbury 2018 (based on data from the 45 and Up study), adjusted to remove PBS costs; applied to patients in the progression free and progressed disease health states over the model time horizon. Adverse event costs were based on the incidence of grade 3 or higher adverse events in ECHO, and hospitalisations costs based on selected AR-DRGs (Round 24 NHCDC Cost Weights 2019-2020 Public Sector report). The average adverse event cost per patient per cycle was derived assuming patients were at risk of adverse events over 60 months. PBS & MBS costs updated to February 2026 costs and wholesaler mark-ups post-July 2026
Discounting	5% per year applied to costs and outcomes
Software package	Excel 2021

Source: Table 3-2, p114 of the July 2026 submission.
ABR = acalabrutinib + bendamustine + rituximab; EQ-5D-3L = EuroQol 5-Dimension, 3-Level health-related quality of life measure; MBS = Medicare Benefits Schedule; MCL = mantle cell lymphoma; NHL = non-Hodgkin's lymphoma; OS = overall survival; PBR = placebo + bendamustine + rituximab; PFS = progression free survival; RR = relapsed/refractory; TOT = time on treatment
Blue shading represents information previously considered by the PBAC.

4.23 The submission used the most recent data cut-off (February 2025) to update OS, PFS, time on treatment (TOT), and time to first subsequent treatment (TFST). In a sensitivity analysis, applying the earlier data cut-off increased the ICER by [redacted]% (from $45,000 to < $55,000 to $55,000 to < $75,000 per QALY) for the COVID-19 censored analysis but reduced the ICER by [redacted]% (from $55,000 to < $75,000 to $55,000 to < $75,000 per QALY) for the FAS analyses.

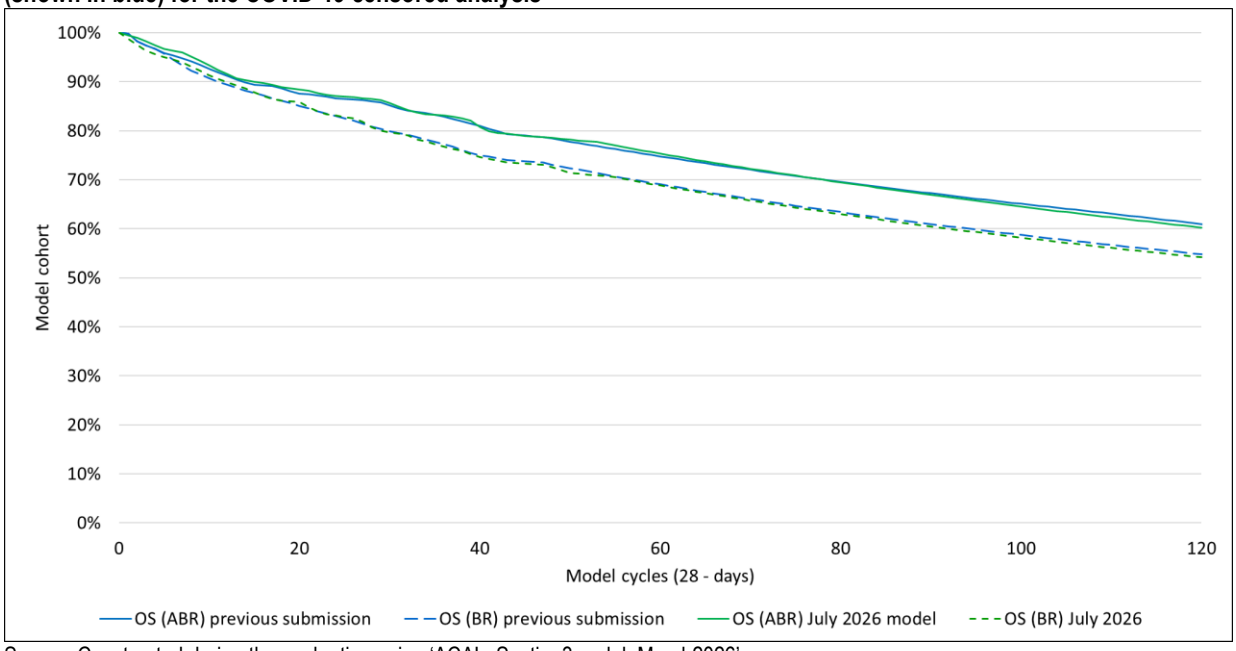
4.24 For the COVID-19 censored analysis, this submission applied the same extrapolation approach as used in the July 2025 submission, whereby Kaplan-Meier (KM) data were used up to the median follow-up of ECHO (45 months in the July 2025 submission and 52 months in this submission), with parametric functions used to extrapolate beyond this period (the same parametric functions were applied, as per the July 2025 submission). The ESC considered the submission did not adequately justify the point of extrapolation and considered the use of KM data until median follow-up may have overestimated the difference between treatments. A sensitivity analysis using KM data up to 72 months for OS (when approximately 20% of patients remain at risk) increased the ICER by [redacted]% for the COVID-19 censored analysis (or [redacted]% for the full analysis set). The ESC considered this sensitivity analysis was informative given use of KM data to a later time-point such as when 20% of patients remain at risk would be more consistent with usual practice, and noting the PBAC guidelines state that time-to-event data should be used in preference to modelled data "up to the time point at which the observed data become unreliable as a result of small numbers of patients remaining event-free" (page 75, Guidelines for preparing a submission to the PBAC, Version 5.0, September 2016). Overall, the ESC considered the ICER was sensitive to the time point chosen and hence there was uncertainty in the estimated ICER. The

pre-PBAC response included KM data up to 72 months for OS in some of its revised economic model scenarios.

4.25 For the COVID-19 censored analysis, the same parametric functions were applied, as per the July 2025 submission (log-normal for OS; log-logistic for PFS, TOT, and TFST). The ESC and PBAC previously noted uncertainties regarding the extrapolations used in the July 2025 model (paragraph 6.37 and 6.40, acalabrutinib PSD, July 2025 PBAC meeting) and suggested that OS extrapolations that resulted in smaller gains in life years would reduce the extent of uncertainty. Given that the same OS extrapolations were applied in this submission, the evaluation and the ESC considered those same issues may apply. The use of alternative extrapolation functions were explored in sensitivity analyses. In addition, the choice of log-normal for OS in this submission was less conservative than Gompertz, resulting in higher long-term survival estimates.

4.26 The application of the updated data in the extrapolation produced changes in the OS and PFS curves compared with the previous submission. For OS, these are summarised in Figure 3 alongside the corresponding KM curves (based on the submission extrapolation).

Figure 3: OS applied in model: July 2026 submission (shown in green) compared with July 2025 submission (shown in blue) for the COVID-19 censored analysis



Source: Constructed during the evaluation using 'ACAL_Section3model_March2026'
ABR = acalabrutinib + bendamustine + rituximab; OS = overall survival; PBR = placebo + bendamustine + rituximab; PFS = progression free survival.

4.27 The submission's model predicted an increase in the incremental modelled OS compared with the July 2025 model (0.425 years; 11.6% increase in the estimated life years gained; Table 8). The ESC considered this increase did not appear to be plausible given the HR for OS in the updated clinical data were almost the same as the earlier

data; that is, the HR for OS was HR = 0.75 (95% CI: 0.53, 1.04) at the February 2024 data cut-off and HR = 0.78 (95% CI: 0.57, 1.06) at the February 2025 data cut-off. The ESC noted there were 21 additional events between the two data cut-offs (ABR: 97 to 108; PBR: 106 to 116 for the FAS). The evaluation and the ESC considered that the observed increase in disaggregated outcomes as shown in Table 8 was due to the impact of applying extrapolation functions to a later point in the Kaplan-Meier curves where the incremental difference in OS was larger between the arms (in the February 2025 versus the February 2024 data cut-offs). The PBAC noted that the pre-PBAC response's revised economic scenarios that extrapolated KM OS data from 72 months helped address this issue.

4.28 Similarly, the submission's model predicted an increase in the incremental modelled PFS years of 0.218 years, equivalent to an 18.6% increase in total PFS years (Table 8), compared with the July 2025 model. The evaluation and the ESC considered this appeared implausibly large given there were only 4 additional progression events between the two data cut-offs (ABR: 57 to 57; PBR: 99 to 103) (see Table 5). Further, the PFS HR improves only modestly (0.59 [95% CI: 0.45, 0.78] vs 0.64 [95% CI: 0.48, 0.84] for 52 months vs the 45 months update), and the observed KM PFS estimates at 24, 36, and 48 months also change only minimally between data cut-offs.

Table 8: Disaggregated outcome results from the submission (discounted) using the COVID-censored analysis

	ABR	PBR	Incremental	Incremental difference vs July-25 submission
July 2026 submission (10-year time horizon)				
Overall survival (year)	6.284	5.859	0.425	0.056 (increased by 11.6%)
Progression free survival (year)	5.667	4.591	1.077	0.218 (increased by 18.6%)
QALYS	5.169	4.770	0.399	0.046 (increased by 13.0%)
July 2025 submission (10-year time horizon)				
Overall survival (year)	6.283	5.904	0.379	-
Progression free survival (year)	5.535	4.616	0.919	-
QALYS	5.159	4.806	0.353	-

Source: Constructed during the evaluation using 'ACAL_Section3model_March2026'
ABR = acalabrutinib + bendamustine + rituximab; PBR = placebo + bendamustine + rituximab; QALY = quality adjusted life year.
Blue shading represents information previously considered by the PBAC.

4.29 The pre-PBAC response stated that with the 72-month OS extrapolation point (as used in some of its revised economic model scenarios) the incremental QALY gain reduced to 0.342 (from 0.399) and was lower than in the July 2025 submission (0.353). The pre-PBAC response argued this was conservative.

4.30 The submission continued to include the costs of subsequent BTK inhibitor use in the placebo arm, but not in the ABR arm arguing that the proposed restriction only allows BTKi use once in a lifetime. The submission also argued that the proportion of ABR patients (5.0% in the updated clinical data versus 4.3% in the previous data cut-off) who received subsequent BTKi therapy was small and thus an adjustment to efficacy (due to BTKi use) was not warranted. The PBAC previously noted that given that

outcomes associated with subsequent BTK inhibitor use could not be removed from the model, it would be appropriate to also include the costs of these therapies in the ABR arm (paragraph 7.12, acalabrutinib Minutes, July 2025 PBAC meeting). The ESC considered that the PBAC's previous advice remained unchanged (i.e. subsequent BTKi costs should be included in the ABR consistent with usage in the clinical trial). To address this, the pre-PBAC response provided revised economic model scenarios that included subsequent BTKi costs in the ABR arm (refer to Table 11).

4.31 While subsequent treatment use was based only on the first-subsequent line of treatment (after ABR or PBR) in the July 2025 submission, this submission also included second- and third-line treatments following ABR or PBR. The probability of patients receiving subsequent treatment in the model relied on extrapolations of TFST (from ECHO), which effectively assumed that second- and third-line treatments are initiated at the same time as first-line subsequent treatment, which is likely to overestimate subsequent treatment costs for both ABR and PBR. Given the higher use of subsequent therapy in PBR relative to ABR (33.4% vs 11.0%), and more patients progressing to later lines (second line 12.4% vs 3.3%; third line 4.7% vs 1.0%), assuming all subsequent treatments occur 'upfront' brought costs forward and reduced discounting. This overestimated the subsequent treatment costs for the PBR arm ($63,562 per patient, compared with $12,886 for the ABR arm) and likely biased results in favour of ABR. The PSCR argued that later line costs were included because the July 2025 PBAC indicated that the previous model did not adequately incorporate the costs and consequences of subsequent anti-cancer treatments. However, the ESC considered the revised approach would only reduce uncertainty if it were appropriately included in the model (i.e. based on when the costs and consequences actually occurred) rather than as an upfront one-off cost. As acknowledged by the PSCR, the ESC considered the submission's approach overestimated costs in the placebo arm.

4.32 The mean duration of subsequent BTKi therapy applied in the economic model was 17.8 months, based on the median duration from an early data cut-off of a study of zanubrutinib in RR MCL. However, results from a later data cut-off found a median treatment duration of 27.6 months (Song et al, 2022[2]). In this data cut-off, 45.3% of patients continued treatment (at a median follow-up of 35.3 months), so the median is likely to underestimate the mean (albeit reflecting usage in a trial setting where patients tend to be relatively fit and generally stay on treatment longer). In a sensitivity analysis with a duration of 27.6 months applied to both the ABR and PBR arms (rather than 17.8 months), the ICER reduced by [redacted]% in the COVID-19 censored analysis (noting the limitations of this analysis, including the issues with the application of subsequent treatment costs). The ESC noted that any changes to

[2] Song Y, Zhou K, Zou D, et al. Zanubrutinib in relapsed/refractory mantle cell lymphoma: long-term efficacy and safety results from a phase 2 study. Blood. 2022 May 26;139(21):3148-3158. Accessed at: https://pmc.ncbi.nlm.nih.gov/articles/PMC9136878/

subsequent BTKi treatment duration in the economic model would require a corresponding change to the 'reduction in subsequent BTKi' use in the RSA (i.e. this would increase the estimated offsets for subsequent BTKi therapy in the financial estimates). The pre-PBAC response included longer durations of subsequent BTKi therapy in some of its revised economic model scenarios, including 27.6 months and 23.4 months (refer to Table 11). The pre-PBAC response stated the latter was based on the ibrutinib PSD, however this appeared to be from the November 2016 submission; for the November 2017 resubmission the PSD states the average treatment duration of ibrutinib was 24.98 months (paragraphs 6.75 and 6.79, ibrutinib (MCL) PSD, November 2017 PBAC Meeting). Refer to paragraph 5.9 for the PBAC's advice.

4.33 In its March 2018 recommendation of ibrutinib for RR MCL, the PBAC advised that an RSA was necessary to achieve cost-effectiveness i.e., the PSD states "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" and that the ICER was reduced due to the assumption that [redacted]% of Commonwealth expenditure on ibrutinib would be rebated through the RSA (paragraphs 12.1 and 6.8, ibrutinib PSD, March 2018 PBAC meeting). Sensitivity analyses using the intended rebate for subsequent lines of BTKi therapy were considered by the ESC and PBAC.

4.34 A summary of the results from the stepped economic evaluation (as presented in the submission) based on the COVID-19 censored analysis is presented in Table 9.

Table 9: Results of the stepped economic evaluation (COVID-19 censored analysis) presented in the submission

Step and component	ABR	PBR	Increment
July 2025 base case			
Costs	$[redacted]	$63,387	$[redacted]
QALYs	6.8891	6.3623	0.5268
Incremental cost per QALY gained			$[redacted][1]
Step 0: PBAC respecified base case as considered in the July 2025 submission (10-year time horizon, and BTK inhibitor costs included in the ABR arm consistent with ECHO)			
Costs	$[redacted]	$50,800	$[redacted]
QALYs	5.1587	4.8062	0.3525
Incremental cost per QALY gained			$[redacted][2]
Step 1: Updated clinical data at median follow-up of 52 months (February 2025 data cut-off)			
Costs	$[redacted]	$50,908	$[redacted]
QALYs	5.1689	4.7703	0.3986
Incremental cost per QALY gained			$[redacted][2]
Step 2: Updated subsequent treatment data with further downstream lines of treatment (Feb 2025 data cut-off)			
Costs	$[redacted]	$53,874	$[redacted]
QALYs	5.1689	4.7703	0.3986
Incremental cost per QALY gained			$[redacted][1]
Step 3: Excluding BTKi from ABR (BTKi once per lifetime)			
Costs	$[redacted]	$53,874	$[redacted]
QALYs	5.1689	4.7703	0.3986
Incremental cost per QALY gained			$[redacted][1]
Step 4: PBS & MBS costs updated to February 2026 costs and wholesaler mark-ups post-July 2026			
Costs	$[redacted]	$52,705	$[redacted]
QALYs	5.1689	4.7703	0.3986
Incremental cost per QALY gained			$[redacted][1]
Step 5: ABS, Life expectancy, 2021-2023 (released 11 November 2025)			
Costs	$[redacted]	$52,706	$[redacted]
QALYs	5.1692	4.7705	0.3987
Incremental cost per QALY gained			$[redacted][1]
Step 6: acalabrutinib effective EMP of $[redacted]			
Costs	$[redacted]	$52,706	$[redacted]
QALYs	5.1692	4.7705	0.3987
Incremental cost per QALY gained			$[redacted][3]

Source: Table 3-39, p184 of the July 2026 submission; compiled during the evaluation using 3.1 ACAL_Section3model_March2026.
ABR = acalabrutinib + bendamustine + rituximab; BR bendamustine + rituximab; ABS = Australian Bureau of Statistics; EMP = Ex-Manufacturer Price; BTKi = Bruton tyrosine kinase inhibitors; MBS = Medicare Benefits Schedule; PBR = placebo + bendamustine + rituximab; PBS = Pharmaceutical Benefits Scheme; QALY = quality adjusted life year.
Blue shading represents information previously considered by the PBAC.
The redacted values correspond to the following ranges:
[1] *$55,000 to < $75,000*
[2] *$75,000 to < $95,000*
[3] *$45,000 to < $55,000*

4.35 Based on the submission's economic model, for every patient treated with acalabrutinib versus placebo (both in combination with bendamustine and rituximab) and followed up for 10 years, the July 2026 submission's economic evaluation based on the analysis with censoring for COVID-19 related deaths (without discounting) estimated that there would be:

- Additional initial treatment costs of $[redacted], additional disease management costs of $433, and additional adverse event management costs of $379.

- Reduced costs of subsequent therapies of $25,522.
- An additional 1.39 years of progression free survival, 0.54 years of overall survival and 0.51 quality adjusted life years.

4.36 A summary of the results from the stepped economic evaluation based on the FAS (per the submission's economic model) is presented in Table 10.

Table 10: Results of the stepped economic evaluation (FAS) presented in the submission

Step and component	ABR	PBR	Increment
July 2025 results			
Costs	$[redacted]	$58,072	$[redacted]
QALYs	5.7263	5.4065	0.3197
Incremental cost per QALY gained			$[redacted][1]
PBAC respecified base case for the July 2025 submission (10-year time horizon, and BTKi costs included in the ABR arm consistent with ECHO)			
Costs	$[redacted]	$47,198	$[redacted]
QALYs	4.5068	4.2574	0.2494
Incremental cost per QALY gained			**$[redacted]**[2]
Step 1: Updated clinical data at median follow-up of 52 months (February 2025 data cut-off)			
Costs	$[redacted]	$47,898	$[redacted]
QALYs	4.5627	4.3255	0.2372
Incremental cost per QALY gained			**$[redacted]**[2]
Step 2: Updated subsequent treatment data with further downstream lines of treatment (Feb 2025 data cut-off)			
Costs	$[redacted]	$50,679	$[redacted]
QALYs	4.5627	4.3255	0.2372
Incremental cost per QALY gained			**$[redacted]**[2]
Step 3: Excluding BTKi from ABR (BTKi once per lifetime)			
Costs	$[redacted]	$50,679	$[redacted]
QALYs	4.5627	4.3255	0.2372
Incremental cost per QALY gained			**$[redacted]**[1]
Step 4: PBS & MBS costs updated to February 2026 costs and wholesaler mark-ups post-July 2026			
Costs	$[redacted]	$49,506	$[redacted]
QALYs	4.5627	4.3255	0.2372
Incremental cost per QALY gained			**$[redacted]**[1]
Step 5: ABS, Life expectancy, 2021-2023 (released 11 November 2025)			
Costs	$[redacted]	$49,505	$[redacted]
QALYs	4.5626	4.3255	0.2372
Incremental cost per QALY gained			**$[redacted]**[1]
Step 6: acalabrutinib effective EMP of $[redacted]			
Costs	$[redacted]	$49,505	$[redacted]
QALYs	4.5626	4.3255	0.2372
Incremental cost per QALY gained			**$[redacted]**[3]

Source: Constructed during the evaluation using 'ACAL_Section3model_March2026'

ABR = acalabrutinib + bendamustine + rituximab; BR = bendamustine + rituximab; ABS = Australian Bureau of Statistics; EMP = Ex-Manufacturer Price; BTKi = Bruton tyrosine kinase inhibitors; FAS = full set analysis; MBS = Medicare Benefits Schedule; PBR = placebo + bendamustine + rituximab; PBS = Pharmaceutical Benefits Scheme; QALY = quality adjusted life year

Blue shading represents information previously considered by the PBAC.

The redacted values correspond to the following ranges:

[1] *$75,000 to < $95,000*

[2] *$95,000 to < $115,000*

[3] *$55,000 to < $75,000*

4.37 The results of key sensitivity analyses are summarised in Table 11, along with the revised economic model scenarios presented in the pre-PBAC response.

Table 11: Sensitivity analyses

Analyses	COVID-19 censored analysis		Full analysis set	
	ICER	% change	ICER	% change
Base case	$[redacted]	-	$[redacted]	-
Discount rate (base case: 5%)				
0%	$[redacted]	-[redacted]%	$[redacted]	-[redacted]%
3.5%	$[redacted]	-[redacted]%	$[redacted]	-[redacted]%
A: Subsequent treatment: BTKi applied to ABR consistent with ECHO (base case: excluded BTKi use for ABR)	$[redacted]	+[redacted]%	$[redacted]	+[redacted]%
B: February 2024 data cut-off clinical data (base case: February 2025 data cut-off)	$[redacted]	+[redacted]%	$[redacted]	-[redacted]%
C: Previous subsequent treatment data based on 1st subsequent treatment (base case: updated subsequent treatment data with further downstream lines of treatment)	$[redacted]	+[redacted]%	$[redacted]	+[redacted]%
D: PSCR's revised base case Updated price of acalabrutinib and ibrutinib in R/R setting – weighted as per PSCR i.e. 2% overall [b]	$[redacted]	+[redacted]%	$[redacted]	+[redacted]%
E: OS extrapolation Gompertz function (base case: log-normal for COVID censored; log-log for FAS)	$[redacted]	+[redacted]%	$[redacted]	[redacted]%
F: Extrapolation of KM curves from 72 months for OS (base case: KM data used for 52 months, based on median follow-up of ECHO)	$[redacted]	[redacted]%	$[redacted]	[redacted]%
G: Duration of subsequent BTK inhibitor therapy 27.6 months applied to both ABR and PBR (base case: 17.8 months applied to PBR) [a]	$[redacted]	[redacted]%	$[redacted]	-[redacted]%
H Duration of subsequent BTK inhibitor therapy 23.4 months applied to both ABR and PBR (base case: 17.8 months applied to PBR) per one of the scenarios in the pre-PBAC response	$[redacted]	[redacted]%	$[redacted]	-[redacted]%
Wholesaler mark-ups as per the July 2025 submission (base case: Wholesaler mark-ups post-July 2026)	$[redacted]	+[redacted]%	$[redacted]	+[redacted]%
Multivariate during evaluation				
A + B	$[redacted]	+[redacted]%	$[redacted]	+[redacted]%
A + C	$[redacted]	+[redacted]%	$[redacted]	+[redacted]%
A + B + C	$[redacted]	+[redacted]%	$[redacted]	+[redacted]%
Multivariate SAs requested by ESC (all include 'D' which was the PSCR's revised base case)				
A + D	$[redacted]	[redacted]%	$[redacted]	[redacted]%
A + D + E	$[redacted]	[redacted]%	$[redacted]	[redacted]%
A + D + F	$[redacted]	[redacted]%	$[redacted]	[redacted]%
A + D + E + F	$[redacted]	[redacted]%	$[redacted]	[redacted]%
A + B + D + E + F	$[redacted]	[redacted]%	$[redacted]	[redacted]%
A + C + D + E + F	$[redacted]	[redacted]%	$[redacted]	[redacted]%
A + B + C + D + E + F	$[redacted]	[redacted]%	$[redacted]	[redacted]%
Pre-PBAC response revised economic model scenarios (all scenarios include 'A' and 'D' i.e. subsequent BTKi costs and updated price of BTKi in RR)				
Extrapolate from 52 months (per submission base case)				
A + D + G (subsequent BTKi for 27.6 months)	$[redacted]	-[redacted]%	$[redacted]	-[redacted]%
A + D + H (subsequent BTKi for 23.4 months)	$[redacted]	-[redacted]%	$[redacted]	-[redacted]%
Extrapolate from 72 months ('F')				

Analyses	COVID-19 censored analysis		Full analysis set	
	ICER	% change	ICER	% change
A + D + F (OS extrapolation from 72 months)	$[redacted][2]	[redacted]%	$[redacted][3]	[redacted]%
A + D + F + G (subsequent BTKi for 27.6 months)	**$[redacted][9]**	**-[redacted]%**	**$[redacted][1]**	**-[redacted]%**
A + D + F + H (subsequent BTKi for 23.4 months)	$[redacted][2]	[redacted]%	$[redacted][2]	-[redacted]%

Source: Compiled during the evaluation using 3.1 ACAL_Section3model_March2026.
ABR = acalabrutinib + bendamustine + rituximab; EMP = ex-manufacturer price; BTKi = Bruton tyrosine kinase inhibitors; COVID-19 = Coronavirus disease 2019; FAS = full analysis set; ICER = incremental cost effectiveness ratio; Inc. = incremental; QALY = quality adjusted life year; KM = Kaplan-Meier; OS = overall survival; SPR = Statutory Price Reductions.
[a] A corresponding change would be required to the 'reduction in subsequent BTKi' use in the RSA.
[b] The evaluation noted that the submission did not include the 5% Statutory Price Reduction (that occurred on 1 April 2026) for subsequent treatment with acalabrutinib in the RR setting. The PSCR acknowledged this and argued the price reduction should be weighted across the three BTKi therapies available in this setting, and thus applied a 2% overall reduction to BTKi costs in the RR setting. This increased the ICER per QALY by [redacted]% (refer to analysis 'D'). The PSCR proposed this as a revised base case. However, the ESC noted this approach still did not account for the intended RSA rebate for BTK inhibitors in the RR setting.
The redacted values correspond to the following ranges:
[1] *$45,000 to < $55,000*
[2] *$55,000 to < $75,000*
[3] *$75,000 to < $95,000*
[4] *$95,000 to < $115,000*
[5] *$15,000 to < $25,000*
[6] *$25,000 to < $35,000*
[7] *$115,000 to < $135,000*
[8] *$135,000 to < $155,000*
[9] *$35,000 to < $45,000*

4.38 In the submission's model, when subsequent BTKi costs were included in the ABR arm (as advised by the PBAC in July 2025), the ICER increased from $45,000 to < $55,000/QALY to $55,000 to < $75,000/QALY for the COVID-19 censored analysis. While this was only slightly higher than the ICER specified by the July 2025 PBAC of $55,000 to < $75,000 per QALY (for the COVID-19 censored analysis), the evaluation and the ESC noted the following issues:

- the updated clinical data highlighted issues with the extrapolation methods applied in the economic model. The evaluation and the ESC considered that the increase in disaggregated outcomes may have been due to the time point at which the extrapolation functions were applied to the Kaplan-Meier curves (refer to paragraph 4.27). The pre-PBAC response used a later time point for extrapolation of OS in some of its revised economic model scenarios;
- use of the updated data cut-off had almost no impact on the model results with the FAS analysis. As such, the ICER for the FAS analysis was higher than previously advised by the PBAC, particularly when the parameters specified by the July 2025 PBAC were applied (i.e. with subsequent BTKi costs included), which resulted in an ICER of $75,000 to < $95,000/QALY (in the submission model). The PBAC previously considered that "acalabrutinib would be acceptably cost-effective with an ICER between $55,000 to < $75,000 per QALY (using full analysis set without censoring for COVID-19) and $55,000 to < $75,000 per QALY (using the COVID-19 censored analysis)" (paragraph 7.13, acalabrutinib Minutes, July 2025 PBAC Meeting); and

- the revised model applied costs for second and third line treatment as a one-time upfront cost using extrapolated time to first subsequent treatment which was likely to overestimate subsequent treatment costs in the placebo arm.

4.39 The ESC noted the results of the following multivariate sensitivity analysis based on the PSCR's revised base case:

- Inclusion of the costs of subsequent BTKi therapy in both arms, consistent with the ECHO trial (given that outcomes associated with subsequent BTKi use could not be removed from the model); and
- Extrapolation of KM curves from 72 months for OS (when approximately 20% of patients remained at risk, per paragraph 4.24).

increased the ICER to $55,000 to < $75,000 for the COVID-censored analysis and $75,000 to < $95,000 for the FAS analysis (scenario A + D + F). The ESC considered that this represented a more plausible analysis for decision-making. The pre-PBAC response included these parameters in some of its revised economic model scenarios.

4.40 The pre-PBAC response also included changes to the duration of subsequent BTKi therapy in some of its revised economic model scenarios, including a duration of 27.6 months.

Drug cost/patient/year

4.41 The drug cost per patient per year is outlined in Table 12. The estimated cost per patient per year reduced from $[redacted] to $[redacted] compared with the July 2025 submission (based on the financial estimates).

Table 12: Drug cost per patient for proposed drug

	ECHO	Economic model	Financial estimates
Daily dose	100 mg twice daily	100 mg twice daily	100 mg twice daily
Adherence[a]	89.08%	89.08%	89.02%
Number of scripts per year[b]	11.62	11.62	11.61
Cost per pack of 56 x 100 mg tablets (proposed effective DPMQ)	$[redacted]	$[redacted]	$[redacted]
Cost per year	$[redacted]	$[redacted]	$[redacted]
Mean duration of treatment	37 months (truncated mean)	54 months	Persistence rates from the economic model were applied (to improve consistency with the economics).
July 2025 submission Cost per year	-	$[redacted]	$[redacted]

Source: Constructed during the evaluation; Section 3.6.1.1; Table 3-22, p166 of the submission; 4.3 ACAL_UCM_March2026 submission
DPMQ = Dispensed Price for Maximum Quantity; mg = milligram.
[a] Relative dose intensity for acalabrutinib in ECHO
[b] Calculated as the estimated number of scripts required per year (365.25/28) adjusted for treatment adherence.

Estimated PBS usage & financial implications

4.42 This submission was not considered by DUSC. The submission presented updated financial estimates for the proposed listing of ABR based on the same mixed

epidemiological and market share approach as in the July 2025 submission. A number of changes were applied to the financial estimates compared with the July 2025 submission:

- Revised effective EMP of $[redacted] for acalabrutinib.
- Application of persistence to the acalabrutinib TOT. This was consistent with the PBAC advice to apply the proportion of patients estimated to remain on treatment in each year (paragraph 6.67, acalabrutinib PSD, July 2025 PBAC meeting). The evaluation noted the estimates appeared to apply the persistence rates incorrectly (e.g. persistence was applied to the incident population from 2021 to 2026 without uptake rates, and the persistence rates from the economic model were applied to the number of continuing patients from the preceding year rather than the starting cohort). Financial estimates with the persistence rates corrected, as calculated by ESC, are shown in Table 14.
- Updated TOT and subsequent treatment utilisation using the ECHO trial data (data cut-off 15-Feb-2025). The evaluation considered this was appropriate and consistent with the approach used in the economic evaluation. As the financial estimates were adjusted using treatment persistence rates, an explicit treatment duration for continuing acalabrutinib patients was not applied.
- Grandfathered patients: increased from < 500 patients in the July 2025 submission to < 500 in the current submission. The submission anticipated that patients would be enrolled in the acalabrutinib patient access program at the time of listing. The PSCR stated 'the eligibility criteria for the patient access program are reflective of the initiation phase of the PBS criteria.'

4.43 The key inputs for the financial estimates are provided in Table 13.

Table 13: Key inputs for financial estimates

Data	Value	Comment
Eligible population		
Incident patients: initiating bendamustine for first line MCL	Yr 1: 222 Yr 2: 233 Yr 3: 245 Yr 4: 257 Yr 5: 270 Yr 6: 284	Updated from previous submission Based on a DUSC analysis (January 2025) of PBS scripts for bendamustine with an Authority code for MCL from July 2018 to June 2024; and the assumption of 5% annual growth. The evaluation considered the assumption of 5% annual growth in the market was uncertain (paragraph 6.64, acalabrutinib PSD, July 2025 PBAC meeting).
Uptake of acalabrutinib	[redacted]% in Yr 1 and Yr 2 [redacted]% in Yr 3 to Yr 6	Uptake rate in Yr 3-Yr 6 was increased from [redacted]% to [redacted]%. The impact of this change on the financial estimates was minor.
Treatment utilisation		
Persistence rates	Yr 1: 73.3% Yr 2: 61.6% Yr 3: 49.9% Yr 4: 45.1% Yr 5: 39.3% Yr 6: 35.2%	Updated from previous submission. The submission applied the treatment persistence rates based on the proportion of patients in the progression free on treatment health state in the 'MarkovTrace ABR' (using the submission's base case economic model for the COVID-censored analysis; the ESC noted that changes to the economic model base case may alter the duration of treatment). The use of persistence rates

Data	Value	Comment
		was consistent with PBAC advice from July 2025 (paragraph 7.14, acalabrutinib PSD, July 2025 PBAC meeting).
Bendamustine/ rituximab induction	100% of patients, 6 cycles (5.52 months)	Unchanged from previous submission.
Duration of rituximab maintenance	ABR: 14.78 months BR: 12.89 months	Unchanged from previous submission.
Compliance	89.02%	Unchanged from previous submission.
Proportion of patients receiving subsequent treatment who will avoid BTKi in RR MCL	85%	Changed from 87.6% in July 2025 PSCR. Based on the proportion of use of BTKi as first subsequent therapies in the placebo arm of the ECHO DCO (February 2025). The evaluation considered this was appropriate and consistent with the PBAC advice (paragraph 6.64, acalabrutinib PSD, July 2025 PBAC meeting).
Proportional use of BTKi in RR MCL	Zanubrutinib 52.08%; ibrutinib 33.48%; acalabrutinib 14.44%	Unchanged from previous submission.
Duration of subsequent BTKi treatment	17.8 months in the submission; changed to scenarios with 27.6 months in the pre-PBAC response	Unchanged from previous submission. The pre-PBAC response proposed a duration of 27.6 months in the economic model (refer to paragraph 4.32) and acknowledged the use of 27.6 months would impact the offsets in the financial estimates and RSA. The PBAC considered this change was reasonable.
Grandfathered patients	[redacted][1]	Increased from [redacted][1] grandfathering patients in July 2025 submission. However, the submission did not appear to reduce the number of scripts for grandfather patients in Year 1 to account for supply received prior to initiating PBS supply. In the ESC-corrected financial estimates, grandfather patients were assumed to receive an average of 6 months of treatment in Year 1, rather than 12 months, assuming that 6 months of treatment would be provided via the patient access program. The PBAC considered that assuming 6 months of treatment in Year 1 was reasonable for grandfathering patients.
Costs		
Acalabrutinib (RR)	$[redacted] (effective DPMQ) (The prices of other BTK inhibitors in the RR setting were based on this.)	Effective DPMQ for acalabrutinib in RR MCL setting (although a rebate was intended through the RSA, refer to paragraph 4.33) based on July 2026 wholesaler mark-ups and a 5% SPR in April 2026. The PSCR stated this was updated to reflect the average SPR across all RR BTKi therapies (i.e. a 2% reduction was applied, consistent with the economic model), and this change was also made in the ESC-corrected financial estimates. The ESC noted this did not include the intended RSA rebates in the RR setting (which were not known to the sponsor).
MBS costs	$126 $100.9 (80%)	Updated based on MBS item 13950. This was appropriate.
Patient copayment	PBS $11.07 RPBS $5.54	Updated based on weighted average of 2025 PBS/RPBS services for acalabrutinib (13325H), bendamustine (10760H, 10763L) and rituximab (13102N, 103090Y) for RR MCL. This was appropriate.

Source: compiled during the evaluation based on Table 4-1 p192, Table 4-2 p194, Table 13, acalabrutinib July 2025 PBAC minutes, Section 4 Workbook
ABR = acalabrutinib + bendamustine+ rituximab; BR = bendamustine+ rituximab; BTKi= Bruton tyrosine kinase inhibitor; CIC = committee in confidence; DCO = data-cut off; DPMQ = dispensed price per maximum quantity; DUSC = Drug Utilisation Sub-Committee; EFC = Efficient Funding of Chemotherapy; FGFR2 = fibroblast growth factor receptor 2; MCL = Mantle cell lymphoma; PAP = patient access program; PBAC =Pharmaceutical Benefits Advisory Committee; PBS = Pharmaceutical Benefits Scheme; PSD = public summary document; RPBS = Repatriation Pharmaceutical Benefits Scheme; RR = relapsed/refractory; SPR = statutory price reduction; Yr = year
Blue shading represents information previously considered by the PBAC.
The redacted values correspond to the following ranges:
[1] *> 500*

4.44 The estimated utilisation and financial implications of listing acalabrutinib for previously untreated mantle cell lymphoma is summarised in Table 14.

Table 14: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Submission						
Number of patients treated [a]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Number of scripts dispensed	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][3]
Estimated financial implications of acalabrutinib						
Cost to PBS/RPBS	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]
Estimated financial implications to other PBS-listed drugs						
Additional rituximab maintenance cost	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]
Reduced use of subsequent BTKis	-$[redacted][5]	-$[redacted][5]	-$[redacted][5]	-$[redacted][5]	-$[redacted][5]	-$[redacted][5]
Net financial implications						
Net cost to PBS/RPBS	**$[redacted][4]**	**$[redacted][4]**	**$[redacted][4]**	**$[redacted][4]**	**$[redacted][4]**	**$[redacted][4]**
Net cost to MBS	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]
Net cost to PBS/RPBS/MBS	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]
ESC-corrected financial estimates [b]						
Number of patients treated	[redacted]	[redacted]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Number of scripts	[redacted][1]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][3]
Cost to PBS/RPBS	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][6]
Reduced use of subsequent BTKis	-$[redacted][5]	-$[redacted][5]	-$[redacted][5]	-$[redacted][5]	-$[redacted][5]	-$[redacted][5]
Net cost to PBS/RPBS	**$[redacted][4]**	**$[redacted][4]**	**$[redacted][4]**	**$[redacted][4]**	**$[redacted][4]**	**$[redacted][4]**
Net cost to MBS	-	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]
Net cost to PBS/RPBS/MBS	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]
Pre-PBAC response changes to use of subsequent BTKis and impact on net cost to PBS/RPBS/MBS						
Reduced use of subsequent BTKi (27.6 month duration)	-$[redacted][5]	-$[redacted][5]	-$[redacted][5]	-$[redacted][5]	-$[redacted][5]	-$[redacted][5]
Net cost to PBS/RPBS	**$[redacted][4]**	**$[redacted][4]**	**$[redacted][4]**	**$[redacted][4]**	**$[redacted][4]**	**$[redacted][4]**
Net cost to MBS	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]
Net cost to PBS/RPBS/MBS	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]
Previous submission (July 2025, PSCR)						
Number of patients treated	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Number of scripts dispensed[a]	[redacted][1]	[redacted]	[redacted][2]	[redacted][3]	[redacted][3]	[redacted][3]
Cost to PBS/RPBS	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][6]	$[redacted][6]	$[redacted][6]
Estimated financial implications to other PBS-listed drugs						
Cost to PBS/RPBS	-$[redacted][5]	-$[redacted][5]	-$[redacted][5]	-$[redacted][5]	-$[redacted][5]	-$[redacted][5]
Net financial implications						
Net cost to PBS/RPBS/MBS	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][6]

Source: Table 4-13 p 206, Table 4-15 p207 of the submission, Section 4 Workbook 'Impact net'; Table 14, acalabrutinib PBAC minutes July 2025

BTKi= Bruton tyrosine kinase inhibitor; MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme

[a] Calculated based on total estimated number of scripts per year divided by 11.61 per year (13.04 scripts per patient per year (365.25 days per year/28 days per script) × treatment adherence of 89.02%.) Section 4 Workbook, Sheet 3a. Scripts proposed (AI117:AN119)

[b] Changes to correct the errors in calculations of persistence were made as outlined in paragraph 4.42. ESC acknowledged these changes may be approximate.

Blue shading represents information previously considered by the PBAC.

The redacted values correspond to the following ranges:

[1] *500 to < 5,000*

[2] *5,000 to < 10,000*

[3] *10,000 to < 20,000*

[4] *$0 to < $10 million*

[5] *net cost saving*

[6] *$10 million to < $20 million*

4.45 In the ESC-corrected financials, the estimated the net cost to the PBS/RPBS of listing acalabrutinib for 1L MCL to be $0 to < $10 million in Year 1 of listing, increasing to $0 to < $10 million in Year 6, a cumulative total of $20 million to < $30 million over the first 6 years of listing compared to $30 million to < $40 million presented in the acalabrutinib July 2025 submission.

4.46 With the pre-PBAC response's changes to the duration of subsequent BTKi therapy (and using the ESC-corrected financials), over 6 years:

- the cost to the PBS/RPBS of 1L acalabrutinib was estimated to be $40 million to < $50 million
- offsets from reduced use of RR BTK inhibitors were estimated to be $20 million to < $30 million (assuming an average 27.6 month duration of BTKi therapy in the RR setting)
- the increased rituximab maintenance costs were estimated to be $0 to < $10 million
- the net cost to the PBS/RPBS was estimated to be $10 million to < $20 million.

Financial Management – Risk Sharing Arrangements

4.47 At its July 2025 meeting, the PBAC considered that an RSA would be required for acalabrutinib in 1L MCL to help manage the risk of use outside the intended restriction particularly as there is potential for use in patients who are eligible for stem cell transplant, noting that cost-effectiveness has not been evaluated in this setting. Further, the July 2025 PBAC considered that, given the cost-effectiveness and financial estimates rely on reduced use of BTKi therapy in the RR MCL setting, a combined RSA across the 1L and RR settings would be preferred to ensure these offsets are realised in practice (given BTK inhibitors are subsidised once per lifetime). The July 2025 PBAC advised that a 100% rebate should apply to any Commonwealth expenditure beyond the agreed estimates (paragraph 7.15, acalabrutinib PSD, July 2025 PBAC meeting).

4.48 The submission's proposed RSA caps were based on:

- assumed growth in BTKi prescriptions in the RR MCL setting; and
- the estimated financial impact in the 1L setting.

<u>RSA RR MCL (growth in the market)</u>

4.49 The current RSA Term in the RR MCL setting ran until July 2023 and then rolled over and the annual expenditure caps are ongoing at the levels of the last year of the deed (2023) with no growth. The RSA has two tiers of expenditure caps, with reimbursement of [redacted]% of expenditure above Subsidisation Cap Threshold 1 and [redacted]% of expenditure above Subsidisation Cap Threshold 2. The cap thresholds were determined following the listing of ibrutinib as the first BTKi subsidised on the PBS. The submission claimed that the current RR MCL caps are no longer appropriate in the

context of a multiproduct BTKi market and should be revised to account for market growth. The submission requested reconsideration of the existing RR MCL caps regardless of whether ABR proceeds to listing for 1L MCL.

4.50 The submission applied two different growth rates to calculate the proposed increase to the RSA in the RR setting:

a) from 2023 to 2026 the submission requested the cap be increased to account for 'catch-up' in the growth of BTKi use for RR MCL; and

b) from cap Year 8 (2025-26) onwards, the submission applied a [redacted]% annual growth rate (sponsor assumption).

4.51 For the first component (a), the submission stated that utilisation of BTKi in RR MCL (acalabrutinib, ibrutinib and zanubrutinib) has increased substantially, with year-on-year growth of: 21% in 2022-23; 32% in 2023-24; and 42% in 2024-25. The submission therefore proposed revised caps, based on the 32%-42% growth in PBS BTKi utilisation. As shown in Table 15, the submission proposed the RR MCL caps be increased to $[redacted] in cap Year 8 (2025-26) with a single tier structure.

Table 15: Calculation of the revised RR MCL caps

	Initial Term cap years		Continued Operation cap years		
	Cap Year 4	**Cap Year 5**	**Cap Year 6**	**Cap Year 7**	**Cap Year 8**
Year	Aug-21 to Jul-22	Aug-22 to Jul-23	Aug-23 to Jul-24	Aug-24 to Jul-25	Aug-25 to Jul-26
Subsidisation cap 1	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
SC2 - SC1 Rebate %	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Subsidisation cap 2	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
> SC2 Rebate %	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Rebate btw SC1 and SC2	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Current RR MCL cap if it were a single tier	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Submission					
RR MCL BTKi growth		21%	32%	42%	[redacted]%
Proposed RR MCL subsidisation caps with "catch-up" growth			$[redacted]	$[redacted]	$[redacted]
Difference between current and proposed RR MCL caps			$[redacted]	$[redacted]	$[redacted]
Pre-PBAC response					
RR MCL BTKi growth			[redacted]%	[redacted]%	[redacted]%
Proposed RR MCL subsidisation caps			$[redacted]	$[redacted]	$[redacted]
Difference between current and proposed RR MCL caps			$[redacted]	$[redacted]	$[redacted]

Source: Table 4.19 p213 of the submission

BTKi = Bruton tyrosine kinase inhibitor; btw = between; MCL = mantle cell lymphoma; PBS = Pharmaceutical Benefits Scheme; RR= relapsed/refractory; RSA = risk share arrangement, SC = subsidisation cap

4.52 The evaluation and the ESC considered that the RR MCL BTKi catch-up growth rates applied were likely to be substantially overestimated as they were derived from only

three years of PBS prescription data, which may not be sufficiently representative of established long-term utilisation patterns, and may instead reflect temporary changes in prescribing behaviour, listing changes and uptake trends. The ESC further considered that increases of this magnitude were not reasonable given a proportion of Commonwealth expenditure on the BTK inhibitors in the RR setting is intended to be rebated through the RSA in order to achieve a cost-effective price. The pre-PBAC response proposed an alternative approach of applying a [redacted]% year-on-year growth from when the current previous RR MCL cap expired (2023), rather than applying the full observed catch-up growth in BTKi utilisation between 2022 and 2024.

4.53 From cap Year 8 (2025-26) onwards, the submission applied a [redacted]% annual growth rate, citing limited utilisation data (July 2025 to January 2026), which the submission considered indicative of plateauing utilisation. The evaluation and the ESC considered that the assumption of [redacted]% annual growth was uncertain, as noted in the previous consideration of acalabrutinib (paragraph 6.64, acalabrutinib PSD, July 2025 PBAC meeting).

RSA 1L MCL

4.54 The submission stated that a rebate below [redacted]% for the 1L population would be appropriate given acalabrutinib is proposed for use in a discrete and clearly identifiable population. However, the evaluation noted that the PBAC previously advised that "a 100% rebate should apply to any Commonwealth expenditure beyond the agreed estimates to help manage the risk of use outside the intended restriction particularly as there is potential for acalabrutinib to be used in patients who are eligible for stem cell transplant, noting that cost-effectiveness has not been evaluated in this setting" (paragraph 7.15, acalabrutinib PSD, July 2025 PBAC meeting). The pre-PBAC response requested a [redacted]% rebate in the first-line setting, which it stated would be consistent with the rebate applied in the [redacted]. The pre-PBAC response reiterated that this was a discrete population and stated there was minimal risk of use outside the intended PBS population.

4.55 The submission proposed the RSA cap for 1L MCL to be based on the 'cost to PBS/RPBS' for acalabrutinib in Table 14 (i.e. $0 to < $10 million in Year 1 increasing to $10 million to < $20 million in Year 6, based on the ESC-corrected financial estimates).

RSA Impact across both RR and 1L MCL

4.56 The submission requested a combined RSA across the 1L and RR settings, consistent with the PBAC's July 2025 advice that this would be preferred to ensure these offsets are realised in practice (given BTK inhibitors are subsidised once per lifetime). However, the pre-PBAC response requested separate caps for each setting stating the 'utilisation in each setting is very different and driven by different patient populations, different treatment options, uncertainties and prices.'

4.57 The submission noted the expenditure thresholds in the RR setting (or the RR component of the combined RSA) would need to be reduced to account for a

reduction in BTKi use in RR MCL due to listing acalabrutinib in 1L MCL. The submission estimated the reduction would be $[redacted] in Year 1 increasing to $[redacted] in Year 6; the magnitude of these offsets were increased in the pre-PBAC response (as a longer duration of subsequent BTKi therapy was assumed) to $[redacted] in Year 6 (applied as a cost-offset in the financial implications, refer to Table 14).

4.58 Table 16 shows the combined impact of the 1L and RR MCL RSA expenditure threshold/s, as proposed in the submission and pre-PBAC response.

Table 16: RSA proposals in the submission and pre-PBAC response – combined impact across 1L and RR MCL

	2027	2028	2029	2030	2031	2032
	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Proposed BTKi RR MCL cap (5% growth)	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Submission (combined expenditure threshold across 1L and RR MCL)						
Acalabrutinib 1L MCL	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]
1L + RR MCL	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Reduction in subsequent BTKi	-$[redacted][2]	-$[redacted][2]	-$[redacted][2]	-$[redacted][2]	-$[redacted][2]	-$[redacted][2]
Combined net cap	**$[redacted]**	**$[redacted]**	**$[redacted]**	**$[redacted]**	**$[redacted]**	**$[redacted]**
Contributions to combined net cap						
1L	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]
RR MCL	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
ESC-corrected financial estimates						
Acalabrutinib 1L MCL	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][3]
1L + RR MCL	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Reduction in subsequent BTKi	-$[redacted][2]	-$[redacted][2]	-$[redacted][2]	-$[redacted][2]	-$[redacted][2]	-$[redacted][2]
Combined net cap	**$[redacted]**	**$[redacted]**	**$[redacted]**	**$[redacted]**	**$[redacted]**	**$[redacted]**
Contributions to combined net cap						
1L	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][3]
RR MCL	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Pre-PBAC response (separate 1L and RR caps in MCL)						
Acalabrutinib 1L MCL [a] Separate cap to RR	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][3]
RR caps with 5% catch-up growth	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Reduction in RR MCL (subsequent BKTi)	-$[redacted][2]	-$[redacted][2]	-$[redacted][2]	-$[redacted][2]	-$[redacted][2]	-$[redacted][2]
• 17.8 months						
• 27.6 months	-$[redacted][2]	-$[redacted][2]	-$[redacted][2]	-$[redacted][2]	-$[redacted][2]	-$[redacted][2]
RR MCL revised cap after accounting for subsequent BTKi use	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
• 17.8 months						
• 27.6 months	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Total spend across both caps	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
• 17.8 month						
• 27.6 months	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]

Source: Table 4.20 p214 of the submission, Section 4 Workbook spreadsheets 'Impact net' and 'RSA'.,
BTKi = Bruton tyrosine kinase inhibitor; MCL = mantle cell lymphoma; RSA = risk share arrangement; RR = relapse/refractory; SC= subsidisation cap; 1L = first line

[a] Based on the ESC-corrected financial estimates, refer to footnote under Table 14.

The redacted values correspond to the following ranges:

[1] *$0 to < $10 million*

[2] *net cost saving*

[3] *$10 million to < $20 million*

4.59 The pre-PBAC response estimated the total expenditure over 6 years (from 2027 to 2032) would be:

- RR MCL: $[redacted] (accounting for: 5% annual growth which would increase expenditure by $[redacted] over 6 years; and cost-offsets for subsequent BTKi use which would reduce expenditure in this setting by $[redacted] over 6 years).
- 1L MCL: $40 million to < $50 million.
- Total expenditure across both caps: $[redacted].

For more detail on PBAC's view, see section 5 PBAC outcome.

5 PBAC Outcome

5.1 The PBAC recommended acalabrutinib (in combination with bendamustine and rituximab (ABR)) for the first line treatment of Stage III or IV mantle cell lymphoma (MCL) in patients who are ineligible for stem cell transplantation. The PBAC acknowledged the clinical need for additional therapies for this population and considered the progression free survival (PFS) benefit demonstrated in the key trial (ECHO) was clinically meaningful. The PBAC considered the pre-PBAC response's updates to the economic model had resolved most of the key uncertainties, and with a further small price reduction acalabrutinib would be acceptably cost-effective. The PBAC advised that, as the cost-effectiveness of the first line listing relies on reduced use of Bruton tyrosine kinase (BTK) inhibitors in the relapsed/refractory (RR) setting, this should be accounted for in a risk sharing arrangement (RSA).

5.2 The PBAC remained satisfied that ABR provides, for some patients, a significant improvement in efficacy over bendamustine and rituximab.

5.3 The PBAC recalled this was the second submission for acalabrutinib for this condition. In its previous consideration (in July 2025), the PBAC had considered that the economic model included uncertain and overly optimistic assumptions and advised that a price reduction would be required for acalabrutinib to be acceptably cost-effective. The PBAC noted that the current submission proposed a lower price than the previous submission (although not at the level implied by the July 2025 recommendation), presented updated data from the ECHO trial, and provided updates to the economic model and RSA proposal.

5.4 The PBAC welcomed the input received via the Consumer Comments facility on the PBS website which highlighted the clinical need for effective treatment options for transplant ineligible patients in the first line setting, especially those with high-risk disease features. The organisations outlined the clinical importance of the PFS benefit observed in the updated ECHO results in terms of preserving quality of life and delaying the impact of relapse, while acknowledging that an OS benefit had not been demonstrated. This was consistent with the comments provided for the previous submission.

5.5 Consistent with its July 2025 consideration, the PBAC considered the proposed place in therapy was appropriate, which was as a first line treatment for advanced stage MCL in patients who are ineligible for stem cell transplant, until disease progression. However, the PBAC reiterated that there is emerging evidence for use of BTK inhibitors in transplant eligible patients (in the first line setting) and therefore a risk of use outside the proposed restriction. The PBAC noted that, over time, use of ABR for the first line treatment of MCL will replace a substantial proportion of use of BTK inhibitors in subsequent lines given these therapies would be limited to once in a lifetime (paragraph 7.5, acalabrutinib PSD, July 2025 PBAC meeting).

5.6 The PBAC maintained its view that the nominated comparator, bendamustine and rituximab, was appropriate.

5.7 The PBAC noted the submission provided a new data cut-off from the ECHO trial that increased the median follow-up by around seven months compared with the July 2025 submission. The HR for PFS was similar compared with the previous data cut-off (for the full analysis set, the HR was 0.69 (95% CI: 0.53, 0.88) in the current submission versus 0.73 (95% CI: 0.57, 0.94) in the previous submission). The PBAC considered that the updated data continued to demonstrate a clinically meaningful PFS benefit. The PBAC noted that overall survival (OS) remained immature and had not reached statistical significance (for the full analysis set, the OS HR was 0.87 (95% CI: 0.67, 1.13)) with less than 40% of patients having experienced an event (i.e. death) in the full analysis set updated data cut-off). Overall, the PBAC maintained its view that the claim of superior comparative effectiveness and inferior safety (versus bendamustine and rituximab alone) was reasonable.

5.8 The PBAC noted that the submission revised the economic model using the updated ECHO trial data and proposed a lower price compared with the July 2025 submission. The submission and the pre-PBAC response adopted the PBAC's previous advice to use a 10-year time horizon and include the costs of subsequent BTK inhibitors in the ARB arm of the model (given the outcomes associated with subsequent BTKi use could not be removed from the economic model). The PBAC considered these changes were appropriate.

5.9 The PBAC considered that the economic model should also include:

- extrapolation of OS from 72 months (when around 20% of patients remained at risk) per some of the pre-PBAC response's revised economic model scenarios. The PBAC considered this was more reasonable than the submission's approach, which had applied KM data until median follow-up and resulted in increased health gains compared with the previous model, which was inconsistent with the updated clinical results which were not materially different.
- a duration of subsequent BTKi therapy of 27.6 months per some of the pre-PBAC response's revised economic model scenarios (rather than 17.8 months used in the submission base case), given this was based on a more recent data cut-off of the zanubrutinib trial.

5.10 The PBAC noted that with these assumptions, the ICER was approximately $35,000 to < $45,000/QALY using the COVID-censored analysis and $45,000 to < $55,000/QALY using the full analysis set. However, the PBAC noted these values increased when the intended cost-effective prices of RR BTK inhibitors (i.e. including the intended RSA rebate) were used. The PBAC previously considered that "acalabrutinib would be acceptably cost-effective with an ICER between $55,000 to < $75,000 per QALY (using the full analysis set without censoring for COVID-19) and $55,000 to < $75,000 per QALY (using the COVID-19 censored analysis)" (paragraph 7.13, acalabrutinib Minutes, July 2025 PBAC Meeting). The PBAC advised that a further small price reduction would be required to achieve an acceptable level of cost-effectiveness.

5.11 The PBAC noted the submission updated the financial estimates to reflect the extrapolated time on treatment curve from the economic model, as advised by the PBAC in July 2025. The PBAC also noted the pre-PBAC response had updated the financial estimates to reflect the longer duration of subsequent BTKi therapy proposed in the economic model. The PBAC considered these changes were reasonable.

5.12 The PBAC reiterated its July 2025 advice that an RSA would be required to help manage the risk of use outside the intended restriction particularly as there is potential for acalabrutinib to be used in patients who are eligible for stem cell transplant, noting that cost-effectiveness has not been evaluated in this setting. The Committee also reaffirmed its previous advice that the structure of the RSA should ensure that RR offsets resulting from the 1L listing are realised in practice (paragraph 7.15, acalabrutinib PSD, July 2025 PBAC meeting).

5.13 The PBAC noted that the pre-PBAC response had presented a revised RSA proposal to include: separate expenditure caps and reimbursement rates for 1L and RR MCL ([redacted]% and [redacted]% respectively); [redacted]% annual growth in the RR setting (regardless of whether ABR proceeds to listing for 1L MCL); and revisions to the RR MCL expenditure cap to account for offsets resulting from the 1L listing (aligned with the longer 27.6 month treatment duration for BTKi therapies in the RR setting, as applied in some of the pre-PBAC response economic and financial models). The PBAC recalled that the RR MCL RSA caps were expected to be exceeded to achieve cost-effectiveness (paragraph 4.33). While the PBAC considered the pre-PBAC response's proposal for [redacted]% year-on-year growth was reasonable in principle, the PBAC advised it would also be appropriate to take into account the performance of the RSA to ensure cost-effectiveness in RR MCL was consistent with what was intended.

5.14 The PBAC recalled that it had previously, in the context of a proposed combined RR/1L RSA, considered that a 100% rebate should apply to any Commonwealth expenditure above the cap (paragraph 7.15, acalabrutinib PSD, July 2025 PBAC meeting). The PBAC considered that if a separate cap structure could still ensure cost-effectiveness in both settings, a lower (i.e. [redacted]% or greater) rebate in the 1L setting may be acceptable. This was because: the 1L setting had more certain population estimates (PBAC had initially considered that the RR population was possibly overestimated, although based on the

best available data at the time) (paragraph 12.3, ibrutinib PSD, March 2018 PBAC meeting); there was also a lower overall expected financial impact in the 1L setting; and the RSA was not explicitly structured to achieve a cost-effective price via over-the-cap reimbursement.

5.15 The PBAC noted that the submission had requested retrospective changes to the RR RSA, however additionally noted that expenditure for past Deed Years had already been accrued, and thus the PBAC's advice related to future arrangements only.

5.16 In terms of the restriction, the PBAC advised that it may be appropriate to amend the proposed restriction to enable grandfather patients to access PBS-subsidised treatment via the induction treatment phase (rather than via a separate grandfather treatment phase, as advised in July 2025).

5.17 The PBAC noted that flow-on changes to the bendamustine PBS restrictions would be required to allow use in combination with acalabrutinib and rituximab.

5.18 The PBAC found that the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were not met. Specifically, the PBAC found that in the circumstances of its recommendation for acalabrutinib:

a) The treatment is not expected to provide a substantial and clinically relevant improvement in efficacy over bendamustine plus rituximab alone, as while clinically relevant improvements in progression-free survival were evident there was no statistically significant difference in overall survival;

b) The treatment is not expected to address a high and urgent unmet clinical need given the availability of other therapies;

c) It was not necessary to make a finding in relation to whether it would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A because one or more of the preceding tests had failed.

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

Outcome:
Recommended

6 Recommended listing

6.1 Add new listings for acalabrutinib as follows:

Induction and continuing treatment

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
ACALABRUTINIB					

acalabrutinib 100 mg tablet, 56	NEW	1	56	5	Calquence

Concept ID (for internal Dept. use)	**Category / Program:** ☒ GENERAL - General Schedule (Code GE)
	Prescriber type: ☒Medical Practitioners
	Restriction type: ☒Authority Required (Telephone/Online PBS Authorities System)
	Prescribing rule level
	Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.
	Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
	Administrative Advice: No increase in the maximum number of repeats may be authorised.
Restriction Summary [new1] / Treatment of Concept: [new1A]	
	Indication: Stage III or IV mantle cell lymphoma
	Treatment Phase: First line therapy - Induction treatment
	Clinical criteria:
	The condition must be previously untreated at the time of initiating treatment with this drug
	AND
	Clinical criteria:
	The treatment must be/have been initiated in combination with both: (i) rituximab, (ii) bendamustine
	AND
	Clinical criteria:
	The condition must be symptomatic prior to initiating treatment with this drug for this indication
	AND
	Clinical criteria:
	Patients must have a WHO performance status of 2 or less prior to initiating treatment with this drug for this indication
	AND
	Clinical criteria:
	Patient must not be eligible for stem cell transplantation
	AND
	Clinical criteria:
	Patient must not have developed disease progression while receiving treatment with this drug for this indication
Restriction Summary [new2] / Treatment of Concept: [new2A]	
	Indication: Stage III or IV mantle cell lymphoma
	Treatment Phase: First line therapy - Continuing treatment
	Clinical criteria:
	Patient must have previously received PBS-subsidised treatment with this drug for this indication
	AND
	Clinical criteria:
	Patient must not have developed disease progression while being treated with this drug for this indication

Flow-on changes

1- Amend an existing clinical criterion and add a new clinical criterion to the bendamustine listings (PBS item codes: 10760H, 10763L) for previously untreated stage III to IV mantle cell lymphoma, to allow triple combination therapy use with rituximab and acalabrutinib.

MEDICINAL PRODUCT **Form**	**PBS item code**	**Max. Amount**	**№.of Rpts**
BENDAMUSTINE Injection	10760H (Public) 10763L (Private)	200 mg	11
Available brands			
BENDAMUSTIN EUGIA (bendamustine hydrochloride 25 mg injection, 1 vial)			
BENDAMUSTINE EUGIA (bendamustine hydrochloride 100 mg injection, 1 vial)			
BENDAMUSTIN HYDROCHLORIDE MEDSURGE (bendamustine hydrochloride 25 mg injection, 1 vial)			
BENDAMUSTINE HYDROCHLORIDE MEDSURGE (bendamustine hydrochloride 100 mg injection, 1 vial)			
Bendamustine Sandoz (bendamustine hydrochloride 25 mg injection, 1 vial)			
Bendamustine Sandoz (bendamustine hydrochloride 100 mg injection, 1 vial)			
Bendamustine Viatris (bendamustine hydrochloride 25 mg injection, 1 vial)			
Bendamustine Viatris (bendamustine hydrochloride 100 mg injection, 1 vial)			

Concept ID (for internal Dept. use)	**Category / Program:** ☒ Section 100 – Efficient Funding of Chemotherapy – Public (IP)/ Private (IV)
	Prescriber type: ☒Medical Practitioners
	Restriction type: ☒Authority Required (STREAMLINED) [7972]
Restriction Summary [7980] / Treatment of Concept: [7972]	
	Indication: Previously untreated stage III or IV mantle cell lymphoma
	Treatment Phase: Induction treatment
	Clinical criteria:
	The condition must be CD20 positive
	AND
	Clinical criteria:
	The condition must be previously untreated
	AND
	Clinical criteria:
	The treatment must be in combination with rituximab; *or*
	The treatment must be in combination with both: (i) rituximab, (ii) acalabrutinib
	AND
	Clinical criteria:
	The condition must be symptomatic
	AND
	Clinical criteria:
	The treatment must be for induction treatment purposes only
	AND
	Clinical criteria:

	Patient must not receive more than 6 cycles (12 doses) of treatment under this restriction
	AND
	Clinical criteria:
	Patient must not be eligible for stem cell transplantation
	Administrative Advice: No increase in the maximum number of repeats may be authorised.

These restrictions may be subject to further review. Should there be any changes made to the restriction the sponsor will be informed.

7 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.

8 Sponsor's Comment

The sponsor had no comment.