

5.13 ZANUBRUTINIB, Capsule 80 mg, Brukinsa[®], BeiGene Aus Pty Ltd

1 Purpose of submission

- 1.1 The Category 1 submission requested a General Schedule Authority Required listing for the treatment of patients with relapsed or refractory (R/R) mantle cell lymphoma (MCL) who have received at least one prior therapy and have a WHO performance status of 0 or 1.
- 1.2 Listing was requested based on a cost-minimisation analysis (CMA) versus ibrutinib.

Table 1: Key components of the clinical issue addressed by the submission (as stated in the submission)

Component	Description
Population	Patients with MCL whose disease has relapsed after or is refractory to at least one prior therapy.
Intervention	Zanubrutinib; 320 mg (four 80 mg capsules) taken orally once daily or 160 mg (two 80 mg capsules) taken orally twice daily until disease progression or unacceptable toxicity.
Comparator	Ibrutinib; 560 mg (4 x 140 mg capsules) once daily until disease progression or unacceptable toxicity.
Outcomes	ORR, duration of response, PFS, OS, frequency of adverse events, in particular atrial fibrillation.
Clinical claim	In patients with R/R MCL, zanubrutinib is as effective as ibrutinib at improving patients' clinical outcomes of ORR, PFS and OS, and superior in terms of safety, particularly for individuals at risk of cardiovascular adverse events, such as atrial fibrillation.

MCL = mantle cell lymphoma; ORR = overall response rate; OS = overall survival; PFS = progression free survival; R/R = relapsed or refractory

Source: Table 1.1, p15 of the submission.

2 Background

Registration status

- 2.1 The submission was lodged under the TGA/PBAC Parallel Process. The TGA application is being considered under the Provisional approval pathway, based on the objective response rate in 2 single-arm trials.
- 2.2 The TGA Delegate's Overview was available at the time of PBAC consideration. The Delegate stated that "While a decision is yet to be made, at this stage I am inclined to approve the registration of the product for the following indication:
- BRUKINSA is indicated for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy."
- 2.3 The submission stated that conversion of the provisional approval to a full approval is intended to be based upon Study BGB-3111-306, a Phase III randomised study currently underway to compare the efficacy and safety of zanubrutinib plus rituximab versus bendamustine plus rituximab in previously untreated participants with MCL

who are not eligible for stem cell transplantation. The study will enrol approximately 500 patients and is estimated to be completed in August 2026. The relevance of Study BGB-3111-306 to the proposed patient population in the current submission is unclear, as the zanubrutinib combination (not monotherapy) is being studied in previously untreated MCL patients.

- 2.4 The Pre-Sub-Committee Response (PSCR) justified the full approval of zanubrutinib based on Study BGB-3111-306, including reference to: (i) evaluation of a closely related but slightly different population allowing demonstration of clinical benefit across a broader MCL patient population, and meaningful activity of zanubrutinib observed in an earlier treatment line likely associated with similarly meaningful activity in later lines; (ii) evaluation of zanubrutinib in the first-line setting allowing generation of long-term tolerability data, which would not be possible in the R/R MCL setting. The PSCR advised that the same approach was agreed with the FDA for the approval of zanubrutinib for R/R MCL under the Accelerated Approval Program in November 2019.

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

3 Requested listing

- 3.1 The requested listing for zanubrutinib is provided below. Secretariat suggested additions are in *italics* and deletions are in ~~striketrough~~.

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MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
ZANUBRUTINIB					
zanubrutinib 80 mg capsule, 120	NEW	1	120	5	Brukinsa
Category / Program: GENERAL – General Schedule (Code GE)					
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners					
Restriction type: <input checked="" type="checkbox"/> Authority Required – immediate/real-time assessment by Services Australia					
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.					
Administrative Advice: Special Pricing Arrangements apply.					
Administrative Advice: For the purposes of administering this restriction, Bruton tyrosine kinase inhibitors are: acalabrutinib [pending outcome], ibrutinib and zanubrutinib [pending outcome]					
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.					
Indication: Mantle cell lymphoma					
Treatment Phase: Initial treatment					
Clinical criteria:					
The condition must have relapsed or be refractory to at least one prior therapy					
AND					
Clinical criteria:					
Patient must have a WHO performance status of 0 or 1					
AND					
Clinical criteria:					
The treatment must be the sole PBS-subsidised therapy for this condition					
AND					
Clinical criteria:					
Patient must not have previously received PBS-subsidised treatment with this drug for this condition					
AND					
Clinical criteria:					
Patient must not have received treatment with another Bruton's tyrosine kinase (BTK) inhibitor for any line of treatment of MCL (untreated or relapsed/refractory disease) Patient must be untreated with Bruton tyrosine kinase inhibitor therapy; or					
Patient must have developed intolerance to another Bruton's tyrosine kinase (BTK) inhibitor of a severity necessitating permanent treatment withdrawal when being treated for relapsed or refractory MCL					
Treatment Phase: Continuing treatment					
Clinical criteria:					
The treatment must be the sole PBS-subsidised therapy for this condition					
AND					
Clinical criteria:					
Patient must have previously received PBS-subsidised treatment with this drug for this condition					
AND					
Clinical criteria:					
Patient must not develop disease progression while receiving PBS-subsidised treatment with this drug for this condition					
Patient must not have developed disease progression while being treated with this drug for this condition.					
Treatment Phase: Transitioning from non-PBS to PBS-subsidised supply – 'Grandfather' arrangements					
Clinical criteria:					
Patient must have received treatment with this drug prior to [insert listing date here]					
Clinical criteria:					

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The condition must have relapsed or be refractory to at least one prior therapy prior to initiating non-PBS-subsidised treatment with this drug for this condition.
AND
Clinical criteria:
Patient must have had a WHO performance status of 0 or 1 at the time non-PBS-subsidised treatment with this drug for this condition was initiated.
AND
Clinical criteria:
The treatment must be the sole PBS-subsidised therapy for this condition
AND
Clinical criteria:
Patient must have been untreated with Bruton tyrosine kinase inhibitor therapy at treatment initiation with this drug; or
Patient must have developed intolerance to another Bruton's tyrosine kinase (BTK) inhibitor of a severity necessitating permanent treatment withdrawal when being treated for relapsed or refractory MCL
AND
Clinical criteria:
Patient must not have developed disease progression while being treated with this drug for this condition.
Administrative advice:
Patients may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a 'Grandfathered' patient must qualify under the 'Continuing treatment' criteria.
Administrative advice:
This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria.

- 3.2 The submission proposed a special pricing arrangement that would include a rebate for zanubrutinib such that the cost-minimisation claim is realised once the effective price for ibrutinib is incorporated.
- 3.3 The proposed restriction is narrower than the suggested TGA indication described in paragraph 2.2, which does not restrict based on WHO performance status or prior treatment with a Bruton tyrosine kinase (BTK) inhibitor.
- 3.4 The proposed restriction is broadly consistent with Study 206 and Study AU-003. While the restriction proposed that patients must have relapsed or be refractory to at least one prior therapy, both studies included patients with 1-5 prior therapies; and while the restriction proposed that patients have a World Health Organisation/Eastern Cooperative Oncology Group (WHO/ECOG) performance status of 0 or 1, the studies had a wider criterion of ECOG status ≤ 2 . These differences are unlikely to be important since most patients in both studies had 1 or 2 prior therapies, and >90% of patients were WHO/ECOG status 0 or 1.
- 3.5 Under the proposed restriction for zanubrutinib, the ESC noted that patients who have received prior treatment with a BTK inhibitor would not be eligible for treatment with zanubrutinib (except in the case of intolerance to ibrutinib of a severity necessitating permanent treatment withdrawal, discussed below). Patients who had received prior treatment with BTK inhibitors (e.g., ibrutinib) were excluded from the key clinical trials, Study 206 and Study AU-003 (R/R MCL cohort). The PBAC considered that treatment with zanubrutinib should be restricted to BTK inhibitor-naïve patients (except in the case of intolerance), and that an analogous criterion should flow on to the restriction for ibrutinib in MCL.

- 3.6 Under the proposed restriction for zanubrutinib, the ESC noted that patients who have developed intolerance to ibrutinib of a severity necessitating permanent treatment withdrawal would be eligible for treatment with zanubrutinib. The PBAC considered that treatment with zanubrutinib should be allowed for patients who have developed such an intolerance and have not experienced disease progression, and that an analogous criterion should flow on to the restriction for ibrutinib in MCL. The PBAC noted that this is consistent with the recommendation for acalabrutinib in R/R chronic lymphocytic leukaemia (CLL) / small lymphocytic lymphoma (SLL) considered at the March 2020 PBAC meeting.
- 3.7 Although provision for transitioning arrangements ('grandfather' arrangements) under an early access program was requested, the number of patients expected to be treated under this program was not provided in the submission. The PSCR stated that there will be approximately 26 patients likely to require transitioning at the time of PBS listing. The PBAC noted that any transitioning arrangements would serve to capture the same eligibility requirements applying to the usual population.

4 Population and disease

- 4.1 MCL is a rare, clinically aggressive B-cell lymphoma that accounts for 6-8% of all non-Hodgkin lymphoma cases. MCL results from the malignant transformation of a B lymphocyte in the outer edge of a lymph node follicle (i.e., the mantle zone). The molecular hallmark and initiating oncogenic event in MCL is the t(11;14)(q13;q32) translocation, leading to overexpression of cyclin D1 and causing cell cycle deregulation.
- 4.2 It is a disease that predominantly affects older men (median age, 68 years), usually presents as late-stage disease, and is associated with a poor prognosis. The National Cancer Institute (2018) estimated 5-year relative survival at 55.9%.
- 4.3 Due to the aggressive nature of the disease, approximately 60-70% of MCL cases are diagnosed at an advanced stage (Stage III or IV) with disseminated lymphadenopathy, splenomegaly, and bone marrow infiltration. Common symptoms include painless lumps in the neck, groin, or armpit; B symptoms (night sweats, persistent fevers, unexplained weight loss); abdominal bloating; diarrhoea; loss of appetite; and fatigue.
- 4.4 MCL patients in Australia have multiple rituximab-based immunochemotherapy options available; however, these regimens are associated with toxicity issues and are often inappropriate for patients in the relapsed or refractory setting who typically have poor overall fitness. Although patients with newly diagnosed MCL often respond to initial treatment, around 85% do not respond or relapse within 10 years.
- 4.5 Ibrutinib was listed on the PBS for R/R MCL in August 2018 (paragraph 2.3, ibrutinib, Public Summary Document (PSD), November 2020 PBAC Meeting).
- 4.6 This submission has proposed zanubrutinib as an alternative treatment to ibrutinib in the R/R MCL setting. Zanubrutinib and ibrutinib are both BTK inhibitors.

- 4.7 Zanubrutinib has also been proposed for patients who receive ibrutinib as a treatment for R/R MCL and develop intolerance requiring permanent treatment withdrawal.

5 Comparator

- 5.1 The submission nominated ibrutinib as the main comparator. The main reasons were:

- Ibrutinib was PBS listed as a treatment for R/R MCL based on superior efficacy and safety compared to immunochemotherapy;
- Ibrutinib is established as the standard of care for patients with R/R MCL;
- Ibrutinib is the only medicine currently listed on the PBS with a specific listing for patients with R/R MCL;
- Ibrutinib and zanubrutinib are both BTK inhibitors.

- 5.2 For patients who have not received treatment with ibrutinib and who are not contraindicated, the nominated comparator is appropriate.

- 5.3 For patients who have received and are intolerant to ibrutinib, or are contraindicated to ibrutinib, immunochemotherapy or supportive care may be a more appropriate comparator.

- 5.4 In the context of the cost-minimisation approach taken by the submission, a further consideration for PBAC is that, under Section 101(3B) of the National Health Act 1953, when the proposed medicine is substantially more costly than an alternative therapy, the committee cannot make a positive recommendation unless it is satisfied that, for some patients, the proposed medicine provides a significant improvement in efficacy and/or reduction of toxicity over the alternative therapy.

- 5.5 While the evaluation considered ibrutinib to be an appropriate comparator, the evaluation also identified that immunochemotherapy (e.g., rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP)) could be replaced in clinical practice, which may be less costly than zanubrutinib.

- 5.6 Acalabrutinib was a near-market comparator and was considered at the July 2021 PBAC meeting in R/R MCL. The submission included a supplementary comparison to acalabrutinib in an appendix to the submission.

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

6 Consideration of the evidence

Sponsor hearing

- 6.1 The Sponsor requested a hearing for this item. The clinician stated that in their prior experience with BTK inhibitors (zanubrutinib, ibrutinib and acalabrutinib), zanubrutinib has good safety and tolerability. The clinician emphasised that ibrutinib is associated with serious adverse events (AEs) such as atrial fibrillation and

hypertension, as well as other AEs such as bruising, bleeding, cramps, rashes, myalgia, and diarrhoea. The clinician explained the importance for R/R MCL patients to be relieved of these side effects that affect their quality of life, and while zanubrutinib also has side effects such as neutropenia and cough, the neutropenia is often mild and can be managed. The clinician considered that although the size of the available MCL studies is small, there were enough patients to show the effect of zanubrutinib is similar to other BTK inhibitors. The clinician referred to the ASPEN study in Waldenström Macroglobulinemia (WM) and the ALPINE study in R/R CLL/SLL and considered that clinicians will use zanubrutinib as the drug of choice in MCL with publication of these safety results. The PBAC considered that the hearing was informative as it provided context to the safety and tolerability of zanubrutinib.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from three organisations via the Consumer Comments facility on the PBS website.
- 6.3 The PBAC noted the advice received from the Leukaemia Foundation, Lymphoma Australia, and Rare Cancers Australia, clarifying the likely use of zanubrutinib in clinical practice. The Leukaemia Foundation noted that the BTK inhibitors such as zanubrutinib, alongside ibrutinib and acalabrutinib, have represented a considerable expansion and improvement in treatment options for people with MCL, and that in particular, zanubrutinib appears to be well tolerated. Lymphoma Australia commented that most MCL patients will relapse after initial remission or may be refractory to first line treatment and access to zanubrutinib will extend patients' lives with manageable side effects. The PBAC noted that this advice was supportive of the evidence provided in the submission and was similar to the advice provided for acalabrutinib for R/R MCL.

Clinical trials and studies

- 6.4 No head-to-head trials comparing zanubrutinib to ibrutinib for patients with R/R MCL were identified.
- 6.5 A direct head-to-head phase III trial of zanubrutinib versus ibrutinib (ASPEN) in another indication (WM) was identified. The key evidence for the safety claim was derived from the ASPEN study.
- 6.6 The submission was based on the following trials and studies:
- Two phase II, single-arm, open-label, nonrandomised studies of zanubrutinib: Study 206 (N=86) and Study AU-003 [N=37] (R/R MCL patients).
 - One randomised, open-label, phase III trial comparing ibrutinib versus temsirolimus: MCL-3001/RAY (N= 139 [ibrutinib arm]).
 - Three phase II, single-arm, open-label studies of ibrutinib: PCYC-1104 (N=111), MCL-2001/SPARK (N=120) and MCL-2002 (N=16).

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6.7 The submission presented the following comparisons of zanubrutinib and ibrutinib:

- The efficacy claim was based on an unanchored matched adjusted indirect comparison (MAIC) of pooled zanubrutinib studies (Study 206 + Study AU-003) and a pooled analysis of three ibrutinib studies (MCL-3001/RAY, PCYC-1104, MCL-2001/SPARK), matched on baseline characteristics.
- A naïve comparison (unanchored and without any matching) of zanubrutinib Study AU-003 with four pooled ibrutinib studies (MCL-3001/RAY, PCYC-1104, MCL-2001/SPARK, MCL2002) was used as a secondary analysis to strengthen the efficacy claim.
- A direct comparison between zanubrutinib and ibrutinib in the ASPEN study formed the basis of the superior safety claim.
- A supplementary naïve comparison of zanubrutinib (Study 206 and Study AU-003) to the near market comparator, acalabrutinib (ACE-LY-004), was also presented in the submission.

6.8 Table 2 provides details of the trials/studies presented in the submission.

Table 2: Trials, studies and associated reports presented in the submission

Trial ID	Protocol title / Publication title	Publication citation
Zanubrutinib		
BGB-3111-AU-003/ Study AU-003/ NCT02343120	A Phase 1, Open-Label, Multiple-Dose, Dose Escalation and Expansion Study to Investigate the Safety and Pharmacokinetics of the BTK Inhibitor BGB-3111 in Patients with B-Cell Lymphoid Malignancies. Clinical Study Report BGB-3111-AU-003. Tam C.S., Wang M., Simpson D. et al. Updated safety and efficacy data in the phase 1 trial of patients with mantle cell lymphoma (MCL) treated with bruton tyrosine kinase (BTK) inhibitor zanubrutinib (BGB-3111).	15 June 2020 <i>Hematological Oncology</i> 2019. 37 (S2): 245-247
BGB-3111-206/ Study 206/NCT03206970	A Single-Arm, Open-Label, Multicenter Phase 2 Study to Evaluate Efficacy and Safety of BGB-3111, a Bruton's Tyrosine Kinase (BTK) Inhibitor, in Subjects with Relapsed or Refractory Mantle Cell Lymphoma (MCL). Clinical Study Report BGB-3111-206 Song Y., Zhou K., Zou D., et al. Treatment of Patients with Relapsed or Refractory Mantle-Cell Lymphoma with Zanubrutinib, a Selective Inhibitor of Bruton's Tyrosine Kinase.	6 June 2019 <i>Clinical Cancer Research</i> . 2020, 26 (16): 4216-4224
BGB-3111-302/ ASPEN/NCT03053440	A Phase 3, Randomized, Open-Label, Multicenter Study Comparing the Efficacy and Safety of the Bruton's Tyrosine Kinase (BTK) Inhibitors BGB-3111 and Ibrutinib in Subjects with Waldenström's Macroglobulinemia (WM). Clinical Study Report BGB-3111-302 Tam CS, Opat S, D'Sa S, et. al. A randomized phase 3 trial of zanubrutinib vs ibrutinib in symptomatic Waldenstrom macroglobulinemia: the ASPEN study.	18 May 2020 <i>Blood</i> . 2020, 136: 2038-50
Ibrutinib		
PCYC-1104/ NCT01236391	Wang ML, Rule S, Martin P, Goy A, Auer R, Kahl BS, Jurczak W, Advani RH, Romaguera JE, Williams ME, Barrientos JC, Chmielowska E, Radford J, Stilgenbauer S, Dreyling M, Jdrzejczak WW, Johnson P,	<i>N Engl J Med</i> . 2013;369(6):507-16.

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Trial ID	Protocol title / Publication title	Publication citation
	<p>Spurgeon SE, Li L, Zhang L, Newberry K, Ou Z, Cheng N, Fang B, McGreivy J, Clow F, Buggy JJ, Chang BY, Beaupre DM, Kunke2l LA, Blum KA. Targeting BTK with ibrutinib in relapsed or refractory mantle-cell lymphoma.</p> <p>Wang ML, Blum KA, Martin P, Goy A, Auer R, Kahl BS, Jurczak W, Advani RH, Romaguera JE, Williams ME, Barrientos JC, Chmielowska E, Radford J, Stilgenbauer S, Dreyling M, Jedrzejczak WW, Johnson P, Spurgeon SE, Zhang L, Baher L, Cheng M, Lee D, Beaupre DM, Rule S. Long-term follow-up of MCL patients treated with single-agent ibrutinib: updated safety and efficacy results.</p>	<p><i>Blood</i>. 2015;126(6):739-45.</p>
MCL-2001/SPARK/ NCT01599949	<p>A Phase 2, Multicenter, Single-Arm Study to Evaluate the Efficacy and Safety of Single-Agent Bruton's Tyrosine Kinase (BTK) Inhibitor, Ibrutinib, in Subjects With Mantle Cell Lymphoma Who Progress After Bortezomib Therapy. Clinical Study Report PCI-32765MCL2001.</p> <p>Wang M., Goy A. et al. Efficacy and Safety of Single-Agent Ibrutinib in Patients with Mantle Cell Lymphoma Who Progressed after Bortezomib Therapy.</p>	<p>6 December 2014</p> <p><i>Blood</i>. 2014;124(21):4471.</p>
MCL-3001/RAY/ NCT01646021	<p>Dreyling M., Jurczak W. et al. Ibrutinib versus temsirolimus in patients with relapsed or refractory mantle-cell lymphoma: An international, randomised, open-label, phase 3 study.</p> <p>Hess G., Rule S., Jurczak W. Health-related quality of life data from a phase 3, international, randomized, open-label, multicenter study in patients with previously treated mantle cell lymphoma treated with ibrutinib versus temsirolimus.</p> <p>Rule S., Jurczak W., Jerkeman M. et al. Ibrutinib versus temsirolimus: 3-year follow-up of patients with previously treated mantle cell lymphoma from the phase 3, international, randomized, open-label RAY study.</p>	<p><i>The Lancet</i>. 2016. 387: 770-778</p> <p><i>Leukemia and Lymphoma</i>. 2017. 58 (12): 2824-2832</p> <p><i>Leukemia</i>. 2018. 32 (8): 1799-1803</p>
MCL-2002/ NCT02169180	<p>Maruyama, D; Nagai, H; Fukuhara, N; Kitano, T; Ishikawa, T; Shibayama, H; Choi, I; Hatake, K; Uchida, T; Nishikori, M; Kinoshita, T; Matsuno, Y; Nishikawa, T; Takahara, S; Tobinai, K. Efficacy and safety of ibrutinib in Japanese patients with relapsed or refractory mantle cell lymphoma.</p>	<p><i>Cancer science</i> 2016; 107 (12): 1785-1790.</p>
Acalabrutinib		
ACE-LY-004/ NCT02213926	<p>An Open-label, Phase 2 Study of ACP-196 (Acalabrutinib) in Subjects With Mantle Cell Lymphoma.</p> <p>Wang M, Rule S, Zinzani PL, Goy A, Casasnovas O, Smith SD, Damaj G, Doorduijn J, Lamy T, Morschhauser F, Panizo C, Shah B, Davies A, Eek R, Dupuis J, Jacobsen E, Kater AP, Le Gouill S, Oberic L, Robak T, Covey T, Dua R, Hamdy A, Huang X, Izumi R, Patel P, Rothbaum W, Slatter JG, Jurczak W. Acalabrutinib in relapsed or refractory mantle cell lymphoma (ACE-LY-004): a single-arm, multicentre, phase 2 trial.</p>	<p>19 May 2017</p> <p><i>Lancet</i>. 2018;391:659-667.</p>
Pooled analysis of ibrutinib studies ^a		
MCL-3001/RAY, PCYC-1104, MCL- 2001/SPARK pooled analysis	<p>Rule S, Dreyling M, Goy A, Hess G, Auer R et al. Outcomes in 370 patients with mantle cell lymphoma treated with ibrutinib: a pooled analysis from three open-label studies.</p>	<p><i>British Journal of Haematology</i> 2017; 179(3): 430-8.</p>

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Trial ID	Protocol title / Publication title	Publication citation
	<p>Rule S, Dreyling M, Goy A, Hess G, Auer R, Kahl B, et al. Ibrutinib for the treatment of relapsed/refractory mantle cell lymphoma: Extended 3.5-year follow up from a pooled analysis.</p> <p>Rule S, Dreyling M, Goy A, Hess G, Auer R, Kahl BS, et al. Median 3.5-Year Follow-up of Ibrutinib Treatment in Patients with Relapsed/Refractory Mantle Cell Lymphoma: A Pooled Analysis.</p> <p>Rule S, Dreyling M, Hess G, Auer R, Kahl B, Cavazos N, et al. Overall survival outcomes in patients with mantle-cell lymphoma (MCL) treated with ibrutinib in a pooled analysis of 370 patients from 3 international open-label studies.</p> <p>Rule S, Dreyling MH, Goy A, Hess G, Auer R, Kahl BS, et al. Long-term outcomes with ibrutinib versus the prior regimen: A pooled analysis in relapsed/refractory (R/R) mantle cell lymphoma (MCL) with up to 7.5 years of extended follow-up.</p>	<p><i>Haematologica</i> 2019; 104(5): E211-E4.</p> <p><i>59th Annual Meeting of the American Society of Hematology (ASH) Blood</i> 2017; 130(Supplement 1).</p> <p><i>Haematologica</i> 2016; 101 (Supplement 1): 155.</p> <p><i>61st Annual Meeting of the American Society of Hematology (ASH) Blood</i> 2019; 134(Supplement 1).</p>

^a Added during the evaluation.

Source: Table 2.5, pp37-38 of the submission.

6.9 The key features of the included evidence are summarised in Table 3.

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Table 3: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population (MCL)	Outcome(s)
Zanubrutinib studies (single arm)					
Study 206	86	Phase II, MC, OL 18.43 mths	Moderate ^a	- One to four previous therapies - ECOG ≤ 2 (0 to 2) - Exclude pts with prior BTK treatment	ORR, CR, PFS, OS, DoR, safety
Study AU-003	37	Phase I, OL, MC 19.42 mths	Moderate ^a	- ECOG ≤ 2 (0 to 2) - Exclude pts with prior BTK treatment in the R/R MCL cohort	ORR, CR, DoR, time to response, PFS, OS
Zanubrutinib vs. ibrutinib (used for safety evaluation only)					
ASPEN	201	Phase III, R, OL, MC 19.47 mths (Zanu) 19.38 mths (IBR)	Low ^b	- ECOG ≤ 2 (0 to 2) - Exclude pts with prior BTK treatment in the WM cohort	CR, PFS, DoR, major response rate, disease burden, AEs
Ibrutinib vs. temsirolimus (only ibrutinib arm used in naïve and MAIC comparisons)					
MCL-3001/RAY	280 (139 IBR)	R, OL, MC 38.7 mths	Unclear ^b	- At least one previous rituximab-containing regimen - ECOG ≤ 1 - Exclude pts with prior BTK treatment	ORR, CR, DoR, PFS, OS, Time to next treatment, Time to response, HRQoL, AEs
Ibrutinib studies (single arm)					
PCYC-1104	111	Phase II, MC 26.7 mths	Moderate ^a	- One to five previous therapies - ECOG ≤ 2	ORR, CR, DoR, PFS, OS, HRQoL, AEs
MCL-2001/ SPARK	120	Phase II, MC 14.9 mths	Moderate ^a	- One to five previous therapies AND at least 1 prior rituximab-containing chemotherapy regimen AND at least 2 cycles of bortezomib therapy - ECOG ≤ 2 - Exclude pts with prior BTK treatment	ORR, CR, PFS, OS, HRQoL, AEs
MCL-2002	16	Phase II, OL, MC n.r. ^b	Moderate ^a	- Relapsed or refractory after at least one prior therapy - ECOG 0 to 1 - Exclude pts with prior ibrutinib treatment	ORR, DoR, PFS, OS, AEs, time to response
Pooled analysis of ibrutinib studies (excluding MCL-2002)^c					
MCL-3001/RAY, PCYC-1004, MCL-2001/ SPARK	370	Pooled analysis 41.4 mths	Moderate ^a	- Per trial populations above	ORR, CR, DoR, PFS, OS, AEs
Acalabrutinib study (single arm; near market comparator)					
ACE-LY-004	124	Phase II, MC 38.1 mths	Moderate ^a	- One to five previous therapies - ECOG ≤ 2 - Exclude pts with prior BTK treatment	ORR, CR, DoR, PFS, OS, Time to response, HRQoL, AEs

n.r.=not reported; AEs = adverse events; BTK = Bruton's tyrosine kinase; CR= complete response; DoR = duration of response; ECOG = Eastern Cooperative Oncology Group; HRQoL = health related quality of life; IBR = ibrutinib; Zanu=zanubrutinib; MC = multi-centre; MCL = mantle cell lymphoma; OL = open label; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; R = randomised; R/R=relapsed or refractory; mths=months; WM = Waldenström macroglobulinemia.

^a The nonrandomised studies were incorrectly assessed using the Cochrane risk of bias tool in the submission, and the overall risk of bias was not stated. Use of the ROBINS-1 assessment tool is recommended in the PBAC guidelines. This tool was used as part of this evaluation.

^b Bias assessed as unclear in November 2017 PBAC meeting (see paragraph 6.11).

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^b Bias assessed using the Cochrane Collaboration's tool for assessing risk of bias.

^c Source: Rule 2019: Rule, Simon, et al. "Ibrutinib for the treatment of relapsed/refractory mantle cell lymphoma: extended 3.5-year follow up from a pooled analysis." *Haematologica* 104.5 (2019): e211.

-The submission did not state the overall level of risk of bias for MCL-3001/RAY and ASPEN. Selection, detection, attrition, and reporting biases were assessed as low, whereas a moderate risk of bias was assigned for the performance bias in the submission.

- The ASPEN trial was conducted in a different disease type at a lower recommended dose of ibrutinib (420mg).

Source: Tables 2.6 to 2.13, pp42-50 of the submission; Table 2.15, 2.17, pp51, 54 of the submission; Tables 2.18 to 2.24, pp56-62 of the submission.

- 6.10 For the majority of studies, the selection, detection, attrition, and reporting biases were assessed as low, whereas a moderate risk of bias was assigned for the performance bias in the submission. The submission did not state the overall level of risk of bias for MCL-3001/RAY and ASPEN.
- 6.11 The MCL-3001/RAY trial was included in November 2016, November 2017, and March 2018 PBAC submissions for ibrutinib as a treatment for R/R MCL. At the November 2017 PBAC meeting, the risk of bias in MCL-3001 was reported as unclear due to the open-label nature of the trial and the large differences in patient discontinuations between the trial arms due to AEs and refusing treatment (paragraph 6.10, ibrutinib PSD, November 2017 PBAC Meeting).
- 6.12 The non-randomised studies were incorrectly assessed using the Cochrane risk of bias tool in the submission, and the overall risk of bias was not stated. Use of the ROBINS-1 assessment tool is recommended in the PBAC Guidelines v5.0. This tool was used as part of the evaluation.
- 6.13 As unblinded single-arm studies, the included trials cannot be considered comparable to a well-performed randomised trial due to unobserved confounders. The risk of bias was considered to be moderate for the non-randomised studies because, as single-arm studies, it is not possible to determine if the results are due to the intervention or baseline prognostic variables.
- 6.14 The included studies differed in terms of inclusion/exclusion criteria, baseline disease characteristics and duration of treatment. The evaluation considered that these differences may confound the results of the naïve comparisons. In particular:
- ECOG status was limited to ≤ 1 in two of the four ibrutinib studies (MCL-3001/RAY and MCL-2002) but ≤ 2 in the zanubrutinib studies (Study 206 and Study AU-003); the requested listing specifies a WHO performance status of 0 or 1.
 - The diagnostic criteria in Study 206 involved using advanced imaging modalities such as positron emission tomography, which can potentially increase the number of patients with a complete response, and to a lesser extent objective response rate. Positron emission tomography was used only in Study 206.
 - Study 206 had slightly younger patients (60.5 years, median age) than the other studies (median age range, 67.5 to 72 years).
 - The median duration of treatment with zanubrutinib (Study 206: 17.75 months and Study AU-003: 15.41 months) was longer than with the ibrutinib studies (PCYC-1104: 8.3 months; SPARK: 8.0 months; RAY: 14.4 months; pooled: 11.1 months).

- Study 206 was conducted exclusively in Chinese patients, and mainly Caucasian patients were recruited in the ASPEN trial.
 - The patient baseline characteristics also varied among the studies in terms of prior stem cell transplant rates, extranodal disease, and the number of prior therapies. However, as shown in Table 6 below, most clinically significant differences, except disease measurement and race, were adjusted for in the MAIC analysis.
 - Furthermore, there may be unobserved confounders. Whilst acknowledging the risk of bias in non-randomised studies, the PSCR noted that both single-arm studies were conducted at multiple-centres, with Study AU-003 conducted globally with a large contribution of centres in Australia. The PSCR also stated that results were consistent between the studies, with a similar overall response rate and median duration of response. Further, the PSCR highlighted the similarities between zanubrutinib and ibrutinib trials in terms of trial design and execution, median follow-up, consistency of dosing and the broad similarities across the baseline characteristics of study participants.
- 6.15 The ESC considered there is potential for historical bias because the ibrutinib trials were conducted earlier than the zanubrutinib trial, and post-progression treatments were likely different.
- 6.16 Non-inferiority margins for ORR, progression-free survival (PFS) and overall survival (OS) were not nominated.

Comparative effectiveness

Whole Trial Population

- 6.17 Table 4 presents the ORR, complete response (CR), PFS, and OS reported for the whole trial population for each study.

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Table 4: Results for ORR, CR, PFS and OS across the studies

Trial/study ID	Zanubrutinib		Ibrutinib				
	Study AU-003	Study 206	MCL-3001/RAY	PCYC-1104	MCL-2001/SPARK	MCL-2002	Pooled Ibrutinib studies (incl. MCL-2002) ^a
N	37	86	139	111	110 ^d	16	376
Median Follow-up, months [Data cut used in the submission]	19.42	18.43	20	15.3	14.9	27	NR
Median Follow-up, months [Latest data cut]	19.42 ^b	18.4 ^b	38.7 ^c	26.7 ^c	14.9 ^b	27 ^b	NR
Overall response rate							
ORR (CR+PR; n (%))	30 (81.1)	72 (83.7)	100 (72.0) 107 (77.0) ^c	75 (67.6) 74 (67.0) ^c	69 (62.7)	14 (87.5)	258 (69.7)
95% CI (%)	64.8, 92.0	74.2, 90.8	20.5, 42.5 69.1, 83.7	58.9, 76.3 57.1, 75.3	53.7, 71.8	65.6, 97.7	64.1, 75.3
Complete response							
CR(data cut used in the submission)	9 (24.3)	59 (68.6)	26 (19) 32 (23) ^c	23 (21.0) 26 (23.4) ^c	23 (19.2) 25 (20.9) ^c	1 (6.3)	73 (18.9)
95% CI (%)	11.8, 41.2	57.7, 78.2	16.0, 30.0 16.3, 30.9	15.2, 30.8 15.9, 32.4	13.3, 28.5 14, 30.9	0.2, 30.2	15.5, 23.8
Progression-free survival							
Median PFS (months)	17.3	22.1	15.6	13.0	10.5	NE	NR
95% CI	(13.2, 30.7)	(17.4, NE)	NR	(7.0, 17.5)	(4.4, 15.0)	(NE,NE)	NR
15 Months PFS rate, % (95% CI)	64.2 (45.3, 78.0)	71.6 (60.4, 80.2)	NR	NR	NR	NR	NR
Overall survival							
Median OS (months)	27.20	NE	30.3	22.5	NR	NR	NR
95% CI	(18.9, 38.2)	(NE, NE)	(NR)	(13.7, NE)			
24-month OS rate, % 95% CI, %	NR	NR	NR	47.0 ^e (37.1, 56.9)	NR	NR	NR

NA= not applicable, NR=not reported; NE=not estimable; ORR=overall response rate; CR=complete response; PFS=progression-free survival; OS=overall survival.

^a Pooled ibrutinib studies= MCL-3001/ RAY + PCYC-1104 + MCL-2001/ SPARK + MCL-2002

^b Later data cuts not reported. The submission used the latest values.

^c For MCL-3001/RAY and PCYC-1104 ibrutinib trials, ORR and CR were available from later data cuts. Source: MCL-3001/RAY latest data was extracted from Rule 2018 (p1801); PCYC-1104 from Wang 2015 p741

^d Response evaluable population (n=110), SPARK CSR p4.

^e Source: Rule 2019, Table 1, p211

Source: Tables 2.37- 2.39, pp79-81 of the submission; Tables 2.42-2.44, pp82-83 of the submission.

- 6.18 For MCL-3001/RAY and PCYC-1104 ibrutinib trials, ORR and CR were available from later data cuts.¹ The latest data were not reported in the submission. Response rates with the extended follow-up data are shown in Table 5 for comparison.
- 6.19 The ORR and CR observed for zanubrutinib were higher than that observed for ibrutinib, individually (except for ORR in MCL-2002) and pooled.
- 6.20 Median PFS values observed for zanubrutinib in Study 206 and Study AU-003 were higher than those observed for ibrutinib in the MCL-3001/RAY, PCYC-1104, and MCL-2001/SPARK studies, individually and pooled. No PFS data were available for MCL-2002.
- 6.21 The median OS value observed for zanubrutinib in study AU-003 (27.2 months) was higher than OS observed for PCYC-1104 (22.5 months) and lower than MCL-3001/RAY (30.3 months). OS data were not presented for the other studies. No additional OS data were found during the evaluation.
- 6.22 Due to the differences in observed and unobserved baseline patient and disease characteristics (paragraph 6.14), any drug treatment effects observed in the whole study populations may be confounded. A MAIC analysis was conducted to adjust for the differences in baseline characteristics.
- 6.23 The submission did not discuss whether expert clinical opinion was sought to select the baseline characteristics to be matched. For unanchored MAICs, all effect modifiers and prognostic variables should be taken into account (Phillippo 2018). There is an unknown risk of bias due to the potential for missing effect modifiers or prognostic variables in the MAIC.
- 6.24 Patient-reported outcomes were not collected in the zanubrutinib trials, Study 206 and Study AU-003. No health-related quality of life results were provided in the submission for the MCL-3001/RAY, PCYC-1104 studies or the pooled analysis of ibrutinib studies.

Matching Adjusted Indirect Comparison (MAIC)

- 6.25 The submission presented an unanchored MAIC using individual patient data from the two zanubrutinib trials (Study 206 and Study AU-003) and aggregated pooled data from PCYC-1104, MCL-2001/SPARK and MCL-3001/RAY (ibrutinib dataset referred to

¹ Rule S, Jurczak W, Jerkeman M, Rusconi C, Trneny M, Offner F, Caballero D, Joao C, Witzens-Harig M, Hess G, Bence-Bruckler I. Ibrutinib versus temsirolimus: 3-year follow-up of patients with previously treated mantle cell lymphoma from the phase 3, international, randomized, open-label RAY study. *Leukemia*. 2018 Aug;32(8):1799-803.

Wang ML, Blum KA, Martin P, Goy A, Auer R, Kahl BS, Jurczak W, Advani RH, Romaguera JE, Williams ME, Barrientos JC. Long-term follow-up of MCL patients treated with single-agent ibrutinib: updated safety and efficacy results. *Blood*. 2015 Aug 6;126(6):739-45.

as “POOLED”). The MAIC was presented as the base case analysis of clinical evidence for effectiveness.

- 6.26 To adjust for differences in baseline characteristics using the entropy based MAIC analysis, patients in trials with individual patient data (IPD) are balanced to create weighted mean baseline characteristics that match those reported for trials without IPD (Hainmueller 2012). In this submission, it is possible that IPD from patients in Study 206 and Study AU-003 were balanced such that the weighted mean baseline characteristics closely matched those reported for patients in the aggregate ibrutinib studies.
- 6.27 The R program code and output for the MAIC analysis were provided with the submission. The log file output matched what was presented in the submission; however, it was not possible to verify the MAIC results because the IPD were not provided.
- 6.28 Table 5 presents a summary of baseline characteristics without adjustment and after matching between zanubrutinib and ibrutinib.

Table 5: Baseline characteristics without adjustment and after matching in the MAIC analysis

	Without adjustment			After matching		
	Zanubrutinib (Study 206 + AU-003), N=123	Ibrutinib POOLED, N=370	p-value	Zanubrutinib (Weighted Study 206 + AU-003) N=38	Ibrutinib POOLED, N=370	p-value
Age at least 65	0.393	0.624	<0.001	0.596	0.624	0.718
Sex	0.746	0.781	0.423	0.770	0.781	0.861
ECOG at least 2	0.049	0.065	0.532	0.084	0.065	0.676
sMIPI: low	0.484	0.238	<0.001	0.262	0.238	0.453
sMIPI: med	0.377	0.443	NA	0.477	0.443	NA
sMIPI: high	0.139	0.319	NA	0.261	0.319	NA
Bulky disease at least 5 cm	0.361	0.489	0.014	0.445	0.489	0.606
Lactate dehydrogenase > uln	0.369	0.538	0.001	0.536	0.538	0.983
Extranodal disease	0.574	0.581	0.887	0.557	0.581	0.778
Bone marrow involvement	0.500	0.457	0.408	0.493	0.457	0.668
Prior line of therapy: at least three	0.320	0.438	0.040	0.422	0.438	0.976
Prior line of therapy: one	0.369	0.268	NA	0.269	0.268	NA
Prior line of therapy: two	0.311	0.295	NA	0.309	0.295	NA
Prior lenalidomide	0.090	0.157	0.071	0.151	0.157	0.937
Prior bortezomib	0.066	0.535	<0.001	0.342	0.535	0.057
Prior stem cell transplant	0.090	0.230	0.001	0.172	0.230	0.375
Prior rituximab	0.795	0.968	<0.001	0.967	0.968	0.939
Prior high-intensity therapy	0.164	0.335	<0.001	0.283	0.335	0.554

sMIPI = simplified mantle cell lymphoma prognostic index; ECOG=Eastern Cooperative Oncology Group; uln=upper limit of normal; MAIC=matched adjusted indirect comparison.

The baseline covariates, which were unbalanced at significance level 0.05, are in bold.

Source: Table 2.50 and 2.51, pp89, 91 of the submission.

- 6.29 None of the variables were significantly different across the studies at the 5% level after matching. The key differences between the baseline characteristics were

adequately adjusted for in the MAIC analysis. However, the proportion of patients with prior bortezomib in the zanubrutinib arm was lower than in the ibrutinib arm and the difference approached the nominal 0.05 significance level (0.34 vs. 0.53 respectively, $p=0.057$). Prior treatment with bortezomib was not found to have any effect on PFS or OS for patients treated with ibrutinib (Rule 2017).²

6.30 Matching for the selected variables resulted in an effective sample size of 38 patients for zanubrutinib, compared with 123 patients (study 206+study AU-003, $N=86+37=123$) in the unbalanced trials. This suggests poor overlap between the zanubrutinib and ibrutinib trial populations. The evaluation considered that the resulting effective sample size may not be sufficient to reliably compare treatments, and it increases uncertainty in the results, as demonstrated by the wider confidence intervals (CIs) after matching in Table 7 below. Small effective sample sizes indicate that results of the MAIC may be unstable (Phillippo 2018).³

6.31 Table 6 presents the overall response rate (ORR) and complete response (CR) rate before and after matching.

Table 6: Summary of response rates (ORR and CR) in MAIC considered studies*

Response Rates	Without adjustment			After matching		
	Zanubrutinib, Unweighted Study 206+ AU-003	Ibrutinib POOLED	Odds Ratio (95% CI) p-value	Zanubrutinib Weighted Study 206 + AU-003	Ibrutinib POOLED ^a	Odds Ratio (95% CI) p-value
ORR (95% CI)	85% (79, 91)	66% (61, 71)	2.92 (1.70, 5.02) 0.000	75% (60, 90)	66% (61, 71)	1.55 (0.61, 3.89) 0.356
CR (95% CI)	34% (26, 42)	20% (16, 24)	2.06 (1.33, 3.20) 0.001	25% (12, 38)	20% (16, 24)	1.33 (0.60, 2.95) 0.477

ORR=objective response rate; CR= complete response; CI=confidence interval.

^a Ibrutinib POOLED= MCL-3001/RAY + PCYC-1104 + MCL-2001/SPARK. MCL-2002 study was not part of the MAIC analysis.

Statistically significant values ($p\text{-value} \leq 0.5$) are in bold.

The log odds ratio was calculated by transforming ORR and CR to the logit scale and assuming normality on the logit scale

Source: Table 2.52, p92 of the submission

* Note that the results presented in Table 6 are derived from ad-hoc/post-hoc analyses conducted by the applicant specifically for the purposes of informing the PBAC consideration. These analyses were not part of the pre-specified statistical plan for Study 206 and Study AU-003. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

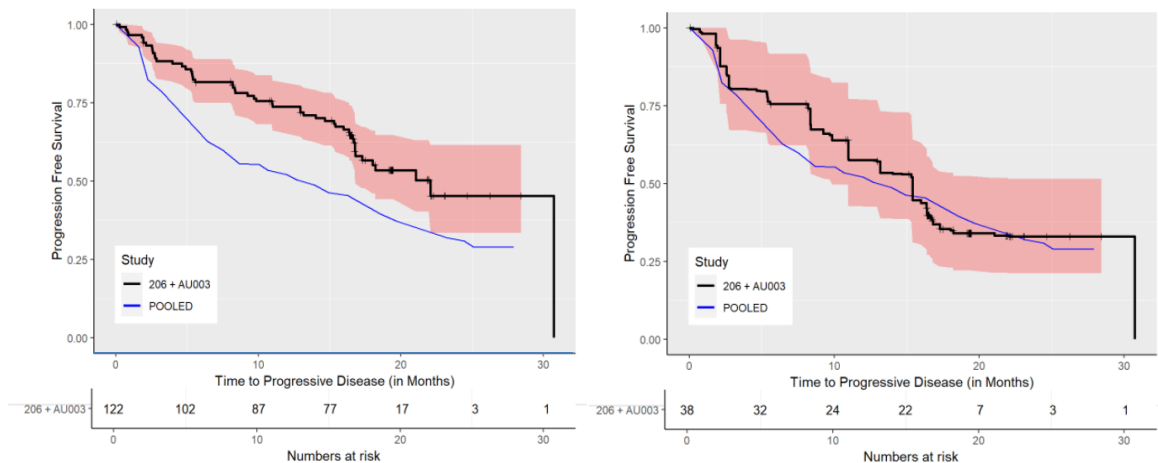
6.32 The submission did not present relative treatment effects for either the before or after matching results. Therefore, the relative treatment effects for ORR and CR were calculated during the evaluation.

² Rule S, Dreyling M, Goy A, Hess G, Auer R, Kahl B, Cavazos N, Liu B, Yang S, Clow F, Goldberg JD. Outcomes in 370 patients with mantle cell lymphoma treated with ibrutinib: a pooled analysis from three open-label studies. British journal of haematology. 2017 Nov;179(3):430-8.

³ PHILLIPPO, D. M., ADES, A. E., DIAS, S., PALMER, S., ABRAMS, K. R. & WELTON, N. J. 2018. Methods for Population-Adjusted Indirect Comparisons in Health Technology Appraisal. Med Decis Making, 38, 200-211.

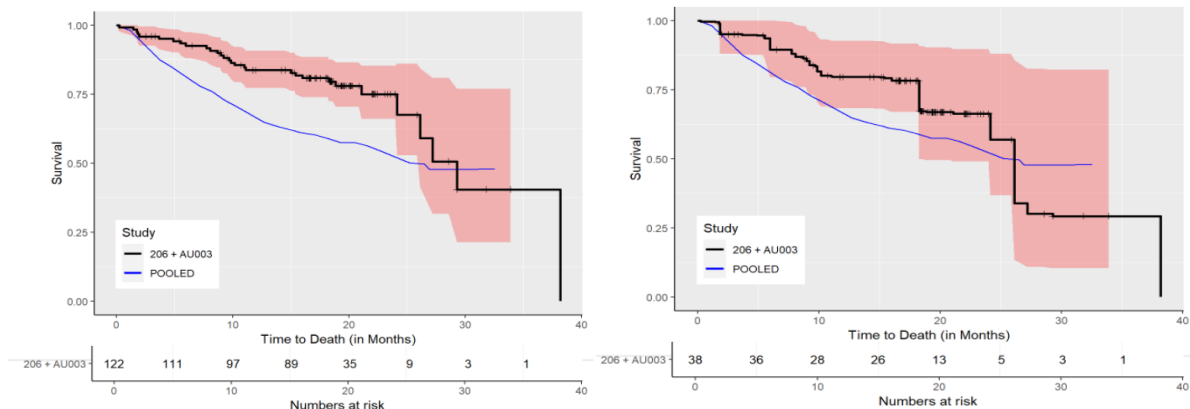
- 6.33 Zanubrutinib was significantly superior to ibrutinib for both ORR and CR in the unadjusted analysis, noting that no treatment effect corresponds to an OR of 1. After matching, no statistically significant differences for ORR (OR=1.55; 95% CI: 0.61, 3.89; p-value=0.356) were observed. Similarly, statistically significant differences for CR (OR= 1.33; 95% CI: 0.60, 2.95; p-value=0.477) were not observed.
- 6.34 Although the point estimates favour zanubrutinib over ibrutinib, the lack of a statistically significant difference in CR and ORR is not sufficient to establish non-inferiority. The evaluation noted that the lower 95% CIs of the OR are lower than the null value of 1 for both ORR and CR: 0.61 and 0.60, respectively.
- 6.35 The PFS and OS Kaplan-Meier curves of the weighted and unweighted analyses are presented in Figures 1 and 2, respectively.

Figure 1: PFS without adjustment (unweighted; left) and after matching (weighted; right) for Study 206+AU-003 and ibrutinib POOLED



PFS=progression free survival. The pink shaded section represents 95% confidence interval for Study 206+ Study AU-003. Source: Figures 2.11 and 2.12, pp92-93 of the submission.

Figure 2: OS before (unweighted; left) and after matching (weighted; right) for Study 206+AU-003 and ibrutinib POOLED



OS=overall survival. The pink shaded section represents 95% confidence interval for Study 206+ Study AU-003. Figures 2.1 and 2.14, pp93-94 of the submission.

- 6.36 The submission stated that zanubrutinib numerically outperformed ibrutinib in terms of PFS in both the weighted and unweighted datasets, with a truncated mean

difference of 4.524 months (without adjustment) and 1.059 months (after matching) by 27.9 months (Figure 1). Similar to PFS, zanubrutinib was claimed to numerically outperform ibrutinib in terms of OS in both the weighted and unweighted datasets, with a restricted mean difference of 3.884 months (without adjustment) and 1.581 months (after matching) by 32.5 months (Figure 2). The submission did not present hazard ratios (HRs) with 95% CIs for PFS or OS.

- 6.37 Subsequently, the Pre-PBAC response provided HRs and 95% CIs between zanubrutinib and ibrutinib for PFS and OS (Table 7), as well as restricted mean survival time (RMST), as an alternative statistic to measure the mean event-free survival time up to a pre-specified clinically important point. The Pre-PBAC response stated that both the naïve and adjusted analyses of HRs and RMSTs for both PFS and OS demonstrate comparable treatment effect between zanubrutinib and ibrutinib, and the analyses are aligned with the other analytical approaches presented and support the claim of non-inferiority.

Table 7: Summary of comparative effectiveness for PFS and OS (Study 206/AU-003 vs PCYC-1103/RAY/SPARK (pooled))

Comparative effectiveness statistics		Naïve comparison (without adjustment)	After matching
		Estimate (95% CI)	Estimate (95% CI)
PFS	RMST difference ^a	4.12 (2.22, 6.01)	0.98 (-1.99, 3.95)
	HR	0.58 (0.43, 0.78)	0.94 (0.65, 1.36)
OS	RMST difference ^b	4.11 (2.32, 5.89)	2.68 (-0.25, 5.60)
	HR	0.50 (0.34, 0.75)	0.77 (0.47, 1.28)

CI=confidence interval; HR=hazard ratio; IPD=individual patient data; OS=overall survival; PFS=progression free survival; RMST= restricted mean survival time.

^a Use min (max (event time from zanubrutinib IPD), max (event time from ibrutinib pseudo IPD)) = 25.124 months as the specified time point for RMST calculation.

^b Use min (max (event time from zanubrutinib IPD), max (event time from ibrutinib pseudo IPD)) = 26.841 months as the specified time point for RMST calculation.

Comparative harms

ASPEN trial

- 6.38 The evidence to support the superior safety claim was based on the direct head-to-head comparison of zanubrutinib with ibrutinib in the ASPEN trial for patients with WM. Despite a different indication, the submission justified the choice of the ASPEN trial due to the lack of a large Phase 3 randomised trial directly comparing two BTK inhibitors in MCL. The evaluation considered this to be reasonable, although the relevance of ASPEN is reduced as it represents a different disease.
- 6.39 Table 8 presents the key safety outcomes in the ASPEN trial.

Table 8: Summary of key adverse events in the ASPEN trial

Patients with events	Zanubrutinib	Ibrutinib	Percent difference %
	N=101	N=98	
	n (%)	n (%)	
Summary safety outcomes, n (%)			
Patients with at least one AE	98 (97.0%)	97 (99.0%)	-2.0
Patients with at least one treatment-related AE	80 (79.2%)	84 (85.7%)	-6.5
Patients with any treatment emergent serious AE	40 (39.6%)	40 (40.8%)	-1.2
AE leading to treatment discontinuation	4 (4.0%)	9 (9.2%)	-5.2
AE leading to death	1 (1.0%)	4 (4.1%)	-3.1
AE leading to dose reduction	14 (13.9%)	23 (23.5%)	-9.6
Patients with at least one AE of special interest	86 (85.1%)	81 (82.7%)	2.4
Any Grade ≥ 3, n (%)			
Any Grade 3 or higher	59 (58.4%)	62 (63.3%)	-4.9
Neutropenia	16 (15.8%)	8 (8.2%)	7.6
Hypertension	6 (5.9%)	11 (11.2%)	-5.3
Thrombocytopenia	6 (5.9%)	3 (3.1%)	2.8
Anaemia	5 (5.0%)	5 (5.1%)	-0.1
Pneumonia	1 (1.0%)	7 (7.1%)	-6.1
Atrial fibrillation and flutter	0 (0.0%)	4 (4.1%)	-4.1
TE SAE \geq Grade 3	59 (58.4%)	62 (63.3%)	-4.9
Treatment related TE SAE	16 (15.8%)	20 (20.4%)	-4.6
Grade ≥ 3, incidence $\geq 5\%$, n (%)			
Neutropenia	16 (15.8)	8 (8.2)	7.6
Hypertension	6 (5.9)	11 (11.2)	-5.3
Pneumonia	1 (1.0)	7 (7.1)	-6.1

AE=adverse event; SAE= serious adverse event; TE=treatment emergent.

Source: Tables 2.45 and 2.47, pp84, 86 of the submission.

6.40 Percentage differences in the incidence of AEs indicated that:

- In terms of the Grade ≥ 3 AEs with greater than 5% frequency, hypertension and pneumonia were higher in the ibrutinib arm whereas higher comparative rates of neutropenia were seen in the zanubrutinib arm (7.6%).
- The zanubrutinib treatment arm had a slightly lower comparative incidence (-4.9%) of patients with any Grade ≥ 3 AEs. Comparatively higher incidence of thrombocytopenia (2.8%) and lower frequency of atrial fibrillation/flutter (-4.1%) was seen in the zanubrutinib arm.
- Comparatively fewer patients discontinued treatment in the zanubrutinib arm than the ibrutinib arm (-5.2%). Similarly, AEs leading to dose reductions were comparatively lower in the zanubrutinib arm (-9.6%).
- Comparatively fewer patients died due to AEs in the zanubrutinib arm compared with the ibrutinib arm (-3.1%). Treatment-emergent serious AEs of \geq grade 3 were also comparatively lower in the zanubrutinib arm (-4.9%).

6.41 Regarding comparative safety, the ESC noted the recent presentation of interim results from a head-to-head trial of zanubrutinib and ibrutinib in patients with R/R

CLL/SLL (ALPINE study⁴). The rate of atrial fibrillation/flutter was significantly lower with zanubrutinib compared to ibrutinib (2.5% vs 10.1%, p=0.0014). Rates of major bleeding, and AEs leading to discontinuation or death were also lower with zanubrutinib. The rate of neutropenia was higher with zanubrutinib, while grade ≥3 infections were lower with zanubrutinib. While results from this trial are only available in abstract form without a full statistical analysis, and relate to a different indication, the ESC considered it might provide additional data for assessment of the safety claim.

Matching Adjusted Indirect Comparison (MAIC)

- 6.42 The submission also presented a MAIC between the pooled zanubrutinib and pooled ibrutinib trials as secondary safety analysis.
- 6.43 Table 9 presents a summary of ≥ Grade 3 AEs for the zanubrutinib trials (Study 206 + Study AU-003) and pooled analysis for the MCL-3001/RAY, PCYC-1104 and MCL-2001/SPARK trials without adjustment and after matching on baseline characteristics.

⁴ First interim analysis of ALPINE study: results of a phase 3 randomized study of zanubrutinib vs ibrutinib in patients with relapsed/refractory chronic lymphocytic leukemia/small lymphocytic lymphoma by Peter Hillmen. EHA Library; Jun 11 2021; https://library.ehaweb.org/eha/2021/eha2021-virtual-congress/330170/peter.hillmen.first.interim.analysis.of.alpine.study.results.of.a.phase.3.html?f=menu=6*broseby=8*sortby=2*media=3*ce_id=2035*marker=1284*featured=17286

Table 9: Summary of key adverse events without adjustment and after matching in the pooled studies

	Without adjustment	After matching		
	Zanubrutinib Study 206+AU-003 %	Zanubrutinib Study 206+AU-003 %	Ibrutinib POOLED %	Percent difference Zanubrutinib after matching vs. ibrutinib POOLED %
THROMBOCYTOPENIA	0.00	0.00	11.08	-11.1
THROMBOCYTOPENIA (GROUP)	0.00	0.00	NA	NA
ABDOMINAL PAIN	9.02	24.19	3.51	20.7
ANAEMIA	0.00	0.00	8.11	-8.1
ARTHRALGIA	0.00	0.00	0.54	-0.5
BACK PAIN	0.00	0.00	1.62	-1.6
CONSTIPATION	0.00	0.00	0.00	0.0
CONTUSION	0.82	3.38	0.00	3.4
COUGH	0.00	0.00	0.00	0.0
DECREASED APPETITE	0.00	0.00	0.81	-0.8
DIARRHOEA	0.82	0.13	3.51	-3.4
DYSPNOEA	0.00	0.00	3.24	-3.2
FATIGUE	3.28	6.17	4.32	1.9
HEADACHE	1.64	0.28	0.00	0.3
HEADACHE (GROUP)	4.10	1.73	NA	NA
MUSCLE SPASMS	0.82	0.16	0.00	0.2
NAUSEA	0.00	0.00	0.27	-0.3
NAUSEA (GROUP)	0.82	0.31	NA	NA
NEUTROPENIA	0.00	0.00	16.49	-16.5
PERIPHERAL OEDEMA	1.64	4.88	1.62	3.3
PNEUMONIA	0.00	0.00	8.92	-8.9
PYREXIA	0.00	0.00	0.81	-0.8

Source: Table 2.54, p95 of the submission.

- 6.44 Out of the 22 AEs \geq Grade 3 groupings seen in the MAIC, 11 had a higher frequency in the pooled ibrutinib dataset compared with 6 in the zanubrutinib studies. The incidence of thrombocytopenia, anaemia, neutropenia, and pneumonia was higher in the pooled ibrutinib dataset. In contrast, the frequency of abdominal pain, contusion and peripheral oedema was higher in the zanubrutinib group.
- 6.45 The superior safety claim made was primarily based on the lower incidence of atrial fibrillation and hypertension in the zanubrutinib arm of the ASPEN trial compared with the ibrutinib arm (Table 8). However, these AEs were not presented in the MAIC safety analysis.
- 6.46 The evaluation considered that inadequate justification for the use of the MAIC methodology for AEs, and the small effective sample size for the zanubrutinib arm increase the uncertainty in the MAIC findings with respect to safety.

Benefits/harms

- 6.47 A summary of the comparative harms for zanubrutinib versus ibrutinib from the ASPEN trial is presented in Table 10.

Table 10: Summary of comparative harms for zanubrutinib and ibrutinib in the ASPEN trial

Harms	Zanubrutinib n/N	Ibrutinib n/N	Event rate/100 patients		RD
			Zanubrutinib	Ibrutinib	
Neutropenia	16/101	8/98	15.8	8.2	7.6
Hypertension	6/101	11/98	5.9	11.2	-5.3
Pneumonia	1/101	7/98	1.0	7.1	-6.1
Atrial Fibrillation and Flutter	0/101	4/98	0	4.1	-4.1

RD=risk difference.

Source: Tables 2.45 and 2.47, pp84, 86 of the submission.

6.48 Based on direct evidence presented by the submission, for every 100 patients with Waldenström Macroglobulinemia (WM) treated with zanubrutinib in comparison with ibrutinib:

- Approximately 8 more patients will experience Grade ≥3 neutropenia;
- Approximately 5 fewer patients will experience Grade ≥3 hypertension;
- Approximately 6 fewer patients will experience Grade ≥3 pneumonia;
- Approximately 4 fewer patients will experience Grade ≥3 atrial fibrillation.

Clinical claim

6.49 The submission described zanubrutinib as at least non-inferior in terms of effectiveness compared to ibrutinib. The key issues were:

- The clinical evidence for zanubrutinib was based on two single-arm open-label nonrandomised studies (Study 206 and Study AU-003). The results from these studies were compared to those from ibrutinib studies by naïve comparisons and an unanchored MAIC.
- The included studies differed in terms of inclusion/exclusion criteria and baseline disease characteristics and duration of follow-up. There may also be unobserved confounders. These differences may confound the results of the naïve study comparisons.

6.50 Non-inferiority margins were not nominated for any of the clinical outcomes used to support the clinical claim: ORR, PFS, or OS. Consistent with the Section 2.4.5 of the PBAC Guidelines (v5.0), the lack of a statistically significant difference is not sufficient to establish non-inferiority. The PSCR stated that a non-inferiority margin was not nominated because there is no widely accepted minimal clinically important difference (MCID) for PFS, OS, overall response, or time to next treatment in this disease area. The PSCR also stated that lack of MCID is consistent with previous submissions in the same drug class, citing the previous recommendation for acalabrutinib in R/R CLL/SLL (paragraph 6.14, acalabrutinib PSD, March 2020 PBAC meeting).

- 6.51 Whilst, based on the information provided, the Sponsor appears to have conducted the MAIC analyses using appropriate methodology, the results of the MAIC comparing zanubrutinib and ibrutinib were considered uncertain because:
- The MAIC analysis resulted in an effective sample size of 38, compared with the original sample size of 123. This suggests poor overlap between the zanubrutinib and ibrutinib trial populations and that the results of the MAIC may be unstable.
 - The MAIC was unanchored. Unanchored MAICs make strong assumptions that are very hard to meet. For example, “conditional constancy of absolute effects” means that the absolute treatment effects are assumed constant at any given level of the effect modifiers and prognostic variables, and all effect modifiers and prognostic variables are required to be known. Post-matching characteristics for variables not chosen for matching were not provided. There is an unknown risk of bias due to the potential for observed and unobserved missing effect modifiers or prognostic variables in the MAIC. The PSCR stated that all relevant available data were used for this MAIC analysis of zanubrutinib vs ibrutinib, with baseline characteristics reported in all 3 ibrutinib studies (PYCY-1104, MCL-2001/SPARK, MCL-3001/RAY) included in the matching. The PSCR acknowledged there may be potential prognostic variables or effect modifiers not included in the matching, however maintained that these could not be included in the MAIC if they were not reported for ibrutinib studies.
- 6.52 The PSCR stated that in the absence of direct comparative evidence, the submission presented multiple approaches for the indirect comparisons, and it was claimed that these multiple analytical approaches demonstrate consistency in outcomes across key trial endpoints, supporting the clinical claim of non-inferiority.⁵
- 6.53 The submission described zanubrutinib as superior in terms of safety compared to ibrutinib. The key issues were:
- Patients in the ASPEN trial that underpinned the safety claim had a different disease, WM.
 - The superior safety claim was based primarily on the lower rates of atrial fibrillation and hypertension in the zanubrutinib arm of the ASPEN trial compared with the ibrutinib arm. However, neither of these AEs was included in the MAIC analysis.
- 6.54 The PSCR maintained that zanubrutinib is superior in terms of safety compared to ibrutinib noting that this claim was supported primarily by a randomised comparison of zanubrutinib with ibrutinib in the ASPEN trial for patients with WM. The PSCR noted that ASPEN was conducted in a different B-cell malignancy (WM), however contended

⁵ Multiple approaches refers to 1) Side-by-side comparison between single-arm zanubrutinib studies (Study 206 and Study AU-003) and the ibrutinib studies (PYCY-1104, MCL-2001/SPARK, MCL-3001/RAY and MCL-2002); 2) A naïve indirect comparison of zanubrutinib and pooled ibrutinib studies; and 3) An unanchored matching adjusted indirect comparison, which was used as a base case to support the clinical claim of non-inferior efficacy.

that the improvements in safety profile are attributable to the improved selectivity for the BTK target of zanubrutinib over ibrutinib and are therefore applicable across multiple indications. The PSCR also noted that a higher dose of ibrutinib (560 mg) is used in MCL than was studied in ASPEN (420 mg) for WM patients, potentially underestimating the risk of AEs and biasing against zanubrutinib. The ESC noted that while the dose of ibrutinib in ASPEN may have potentially biased against zanubrutinib, use of lower doses for the comparator does not automatically infer underestimation of AEs. The ESC agreed with the submission that it was informative to provide data from the ASPEN trial for assessment of the safety claim.

- 6.55 The PSCR stated that the MAIC is also broadly supportive of the superiority claim for safety but is limited because it is only able to present AEs that were commonly reported between the studies.
- 6.56 While acknowledging the uncertainty associated with the evidence presented in the submission, the ESC considered that non-inferior efficacy of zanubrutinib to ibrutinib may be reasonable. However, the ESC considered that the claim of superior safety to ibrutinib was not supported because of the uncertain application of the MAIC methodology to AE data and the randomised safety comparison being in a different B-cell malignancy. The ESC considered that a claim of non-inferior safety would be more appropriate. The Pre-PBAC response maintained that the claim of superior safety was reasonable.
- 6.57 The PBAC considered that while the comparison between zanubrutinib and ibrutinib using single arm data was uncertain due to the issues discussed in paragraphs 6.49, 6.50 and 6.51, both the naïve comparison and the MAIC analysis were consistent with non-inferiority and that on balance, zanubrutinib is likely to have similar effectiveness to ibrutinib in R/R MCL.
- 6.58 The PBAC considered the claim that zanubrutinib is superior in terms of comparative safety compared with ibrutinib was not adequately supported. The PBAC acknowledged the data in indications other than MCL suggested that treatment with zanubrutinib may be associated with a lower rate of AEs compared with ibrutinib, including lower rates of atrial fibrillation and hypertension, however based on the limited single arm data currently available for zanubrutinib in MCL, the PBAC did not accept the superiority claim.

Economic analysis

- 6.59 The submission presented a CMA of zanubrutinib versus ibrutinib based on the claim of non-inferior efficacy and superior safety. A cost-minimisation approach is consistent with the clinical claim.
- 6.60 The equi-effective doses were estimated as:
- Zanubrutinib 320 mg (four 80 mg capsules) taken orally once daily or 160 mg (two 80 mg capsules), taken orally twice daily until disease progression or unacceptable toxicity, and

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- Ibrutinib 560 mg taken orally once daily until disease progression or unacceptable toxicity.
- 6.61 The proposed equi-effective doses were consistent with the medicine doses and treatment regimens in the included studies and the TGA Product Information for zanubrutinib and ibrutinib.
- 6.62 At the latest data cut, the median duration of treatment was longer for zanubrutinib (Study 206: 17.8 months with median follow-up of 18.4 months and Study AU-003: 15.4 months with median follow-up of 19.4 months) than for ibrutinib (14.4 months with a median follow-up of 38.7 months in the MCL-3001/RAY study). This does not support the assumption of equal duration of treatment with zanubrutinib and ibrutinib, although any difference may be due to differences in patient baseline characteristics between the zanubrutinib and ibrutinib studies. Mean duration of treatment for the MCL-3001/RAY trial is unpublished. Mean durations of treatment were not reported in the submission for Study 206 and Study AU-003, but were available in the clinical study reports, noting there was a shorter follow-up time in the zanubrutinib studies as compared with MCL-3001/RAY trial.
- 6.63 No additional costs/or cost offsets were claimed. The CMA results included the drug costs only.
- 6.64 As a secondary analysis, a potential cost saving of \$ [REDACTED] per patient per 30 days was estimated with zanubrutinib use due to the reduced costs of treating atrial fibrillation and pneumonia, despite increased costs of treating neutropenia. In its consideration of acalabrutinib as treatment for patients with R/R CLL/SLL, the PBAC considered that the cost-minimisation analysis should not include AE costs due to the unreliability of the data presented in the MAIC (paragraph 7.11, acalabrutinib PSD, March 2020 PBAC meeting).
- 6.65 The PBAC considered that to ensure the cost per patient treated with zanubrutinib is no more than for ibrutinib, that cost offsets for AEs should not be included in the CMA given the clinical uncertainty associated with the inputs informing these costs.
- 6.66 The results of the cost-minimisation analysis based on the published AEMP of ibrutinib are presented in Table 11.

Table 11: Results of the cost-minimisation analysis

Component	Zanubrutinib	Ibrutinib
Ex-manufacturer price (published)	\$11,511.05 ^a	\$11,511.05 ^a
Days per pack	30	30
Medicine cost per day ^b	\$383.70	\$383.70

^a The effective price is subject to special pricing arrangement.

^b Medicine cost per day calculated by dividing \$11,511.05 by 30.

Source: Table 3.10, p111 of the submission.

- 6.67 The ESC noted that for patients who have developed an intolerance to ibrutinib necessitating permanent treatment withdrawal, and then go on to receive zanubrutinib as per the requested listing (paragraph 3.6), the duration of therapy for

zanubrutinib after initial exposure to ibrutinib is unknown and has not been accounted for in the CMA.

- 6.68 The PBAC noted that the cost-minimisation approach must establish that the cost per patient for zanubrutinib would be no more than the cost per patient of ibrutinib. The cost per patient takes into account the mean equi-effective doses of the new intervention and the alternative therapy, and accounts for any difference in the median duration of treatment. Where these cost per patient calculations are uncertain, the guiding principle is that the Australian Government should not bear the financial risk of this uncertainty because the Australian population already has access to therapy that is at least as effective and safe.
- 6.69 The ESC noted that the CMA draws from a limited clinical evidence base that used naïve comparisons and an unanchored MAIC. To limit the consequences of the clinical uncertainty, the ESC recommended adjustment of the duration of treatment included in the CMA.
- The time on treatment for each agent should reflect the clinical trial data: median of 17.8 or 15.4 months for zanubrutinib at 18.4 or 19.4 months median follow-up, for Study 206 and AU-003, respectively, and 14.4 months for ibrutinib at 38.7 months median follow-up. The ESC considered that the assumed equal duration of treatment for zanubrutinib and ibrutinib (14.4 months) was not justified given the median length of treatment in the pivotal zanubrutinib studies that established non-inferiority was longer (17.8 months for Study 206 and 15.4 months for AU-003). On this issue, the PSCR commented that the assumption of equal duration of treatment is consistent with the clinical claim of non-inferiority in PFS, given that patients are treated to disease progression.
- 6.70 While the PBAC agreed with the ESC that equal duration of treatment for zanubrutinib and ibrutinib was not adequately supported, the PBAC considered that the follow-up in the zanubrutinib trial was too short (median of approximately 19 months versus 39 months for ibrutinib) to provide a reliable and comparable estimate of the likely treatment duration for zanubrutinib. The median duration for zanubrutinib was also only slightly longer than the median follow-up for Study 206, and trial AU-003 was small. The PBAC therefore recommended that, after adjustment for equi-effective doses, zanubrutinib should be listed on the PBS at a cost per day that is no higher than the cost per day of other BTK inhibitors recommended for listing by the PBAC for the treatment of MCL.

Drug cost/treatment course

- 6.71 The proposed published AEMP for zanubrutinib was \$ [REDACTED] (DPMQ = \$ [REDACTED], based on 1 July 2021 fees and mark-ups, and was previously \$ [REDACTED] at the time of the evaluation). The submission assumed an equal duration of treatment with zanubrutinib and ibrutinib (14.4 months), resulting in a cost per treatment course of \$ [REDACTED] (assuming 1 month is 30.44 days). Increasing

the median duration of treatment to 17.8 months per Study 206 increases the cost per treatment course to \$ [REDACTED] at the proposed price.

Estimated PBS usage & financial implications

- 6.72 DUSC considered this submission.
- 6.73 A combination of epidemiological and market share approaches was used to estimate the utilisation and financial impacts associated with the PBS listing of zanubrutinib.
- 6.74 For the market share approach, commissioned research data were used to estimate the number of zanubrutinib scripts directly substituting ibrutinib. Using the epidemiological approach, additional patients who are eligible for a BTK inhibitor but are currently not treated with ibrutinib due to the risk of atrial fibrillation were assumed to benefit from zanubrutinib treatment.
- 6.75 Table 12 shows the key inputs used in the financial estimates.

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Table 12: Key inputs for financial estimates

Data type	Value	Data sources	Comment
Utilisation of ibrutinib for R/R MCL – Year 2020	2,514	PBS data from Medicare Statistics for ibrutinib, item number 11419B between Jan-20 to Dec-20 ^a	The evaluation considered the data source to be appropriate, although the DUSC commented that due to the effects of COVID-19, scripts from 2019 may be more appropriate.
Rate of yearly growth in R/R MCL total market scripts	3.28%	Based on the ibrutinib script growth through 2020.	This assumption is likely underestimated. The growth rate in ibrutinib scripts between 2019 and 2020 was 26%, suggesting that a steady-state is not reached yet.
Duration of treatment in epidemiological model	17 months	Study 206	The evaluation considered this was reasonable, although the median treatment for Study 206 was 17.8 months. DUSC commented that it is unclear why a different duration was used.
Compliance	100% first year, 95% second year	Assumption	DUSC commented that it was unclear why compliance dropped in the second year.
Increase in R/R MCL market size due to zanubrutinib listing	4.39%	Based on the DUSC review (DUSC, 2016). ^b Assumes an additional 7 patients with previous atrial fibrillation and contraindicated for ibrutinib. Approximately 50% of these patients (roughly 3 patients) were estimated to receive zanubrutinib every year. ^c	DUSC commented it was unclear how this figure (4.39%) was derived from the Novel Anticoagulants 2016 DUSC report. Age adjusted prevalence of atrial fibrillation included in report by Sturm et al. (2002) for those aged 60-69 years, 70-79 years and 80 years and over were 4.2%, 10.9% and 14.8%, respectively. DUSC considered as MCL patients are generally older, the atrial fibrillation rate used in the submission is likely underestimated. The Pre-PBAC response revised the estimate to an age-adjusted prevalence of 11.5%.
Script ratio	1.0	Assumption based on same median duration of treatment and same relative dose intensity.	DUSC commented the validity of safety claims were unclear as treatment duration would be longer for zanubrutinib than for ibrutinib. Treatment duration based on trials would be more appropriate.
Grandfathered patients	Nil	Not included in the budget impact estimates.	The proposed listing included grandfathered patients. It may not be reasonable to exclude grandfathered patients from the budget impact estimates. If patients in the patient access program are contra-indicated for or intolerant to ibrutinib, they will grow the market when grandfathered. The PSCR stated that there will be approximately 26 patients eligible for the grandfather restriction at the time of PBS listing.

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Uptake rate (market share of zanubrutinib after listing)	Yr 1: ██████% Yr 2: ██████% Yr 3: ██████% Yr 4: ██████% Yr 5: ██████% Yr 6: ██████%	Assumption based on commissioned data (number of respondents=27, 93% response rate).	This is uncertain. These estimates included MCL and Waldenström Macroglobulinemia patients treated with zanubrutinib and acalabrutinib for multiple lines of therapy. The results were unable to be verified (pp7-12 of the Attachment IQVIA survey). If zanubrutinib is perceived to have a favourable safety profile compared to other BTK inhibitors, the market share will be underestimated. The Pre-PBAC response clarified that the provided market research data comprised different modules segregated by indication.
Ibrutinib published DPMQ	\$11,667.93 (Latest price: \$11,672.21)	PBS item number 11419B.	The DPMQ presented in the submission was \$11,667.93, slightly less than the latest PBS DPMQ of \$11,672.21. Prices as per the latest PBS values were added in the commentary.
Zanubrutinib DPMQ	\$11,667.93 (Latest price: \$11,672.21)	Requested price	Assumed to be equal to ibrutinib.
Cost to MBS	Nil	MBS online	This is reasonable. A potential cost saving of \$12,576 over six years was estimated by the submission due to fewer resources required to manage adverse events with zanubrutinib versus ibrutinib. However, the CMA results presented in section 3.4 of the submission did not include the MBS cost savings. MBS cost savings were included as a potential cost-saving scenario only.
Cost of hospitalisations for adverse events	Nil	NHCDC Round 22 Cost weight tables, DRG Version 10	This is reasonable. A potential cost saving of \$116,347 over six years was estimated by the submission due to fewer hospitalisations. However, the CMA results presented in section 3.4 of the submission did not include the hospitalisation costs. These costs were included as a potential cost-saving scenario only.

DPMQ= Dispensed Price for Maximum Quantity; BIM = budget impact model; MCL – Mantle Cell Lymphoma; PBS = Pharmaceutical Benefits Scheme.

^a 2,514 was derived from Ibrutinib use Jan-20 to Dec-20, source: financial worksheet PBS_Data_MCL_monthly.

^b The baseline rate of atrial fibrillation, 4.39%, was taken from the age-adjusted prevalence of the general population provided in the Drug Utilisation Sub-committee report (DUSC, 2016). Source: DUSC (2016) Novel Oral Anticoagulants: Predicted vs actual analysis - Drug utilisation sub-committee (DUSC)

^c The lower estimate was derived from the incidence rate for MCL of 0.5 per 100,000 persons (340 cases) in Australia (Cheah 2019) and the upper estimate of 1.73 per 100,000 persons (450 cases). For the epidemiological model, the midpoint of these two estimates was used, 1.12 per 100,000 persons. The relapse rate (from incident MCL to R/R MCL) was estimated as 50% (Attachment IQVIA Survey MCL). Source: Table 4.1, p113 of the submission.

6.76 Table 13 presents the estimated financial implications for the listing of zanubrutinib based on the published price of ibrutinib (DPMQ \$11,667.93). The financial estimates were updated using the latest DPMQ price (\$11,672.21) for ibrutinib during the evaluation.

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Table 13: Estimated use and financial implications (published DPMQ)

	Year 1 2022	Year 2 2023	Year 3 2024	Year 4 2025	Year 5 2026	Year 6 2027
Estimated extent of use						
Number of zanubrutinib scripts dispensed	█ ¹	█ ²	█ ²	█ ²	█ ²	█ ²
Number of ibrutinib scripts offset	-█ ¹	-█ ²	-█ ²	-█ ²	-█ ²	-█ ²
Estimated financial implications of zanubrutinib						
Cost to PBS/RPBS less co-payments	\$█ ³	\$█ ³	\$█ ⁴	\$█ ⁴	\$█ ⁴	\$█ ⁴
Estimated financial implications for ibrutinib						
Cost to PBS/RPBS less co-payments	-\$█ ³	-\$█ ³	-\$█ ⁴	-\$█ ⁴	-\$█ ⁴	-\$█ ⁴
Net financial implications						
Net cost to PBS/RPBS (as stated in the submission)	\$█ ³	\$█ ³	\$█ ³	\$█ ³	\$█ ³	\$█ ³
Net cost to PBS/RPBS (latest DPMQ) ^a	\$█ ³	\$█ ³	\$█ ³	\$█ ³	\$█ ³	\$█ ³
Net cost to MBS	\$0	\$0	\$0	\$0	\$0	\$0

PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme; DPMQ= Dispensed Price for Maximum Quantity; MBS=Medicare Benefits Scheme.

^a Net cost to R/PBS calculated as per the latest DPMQ for ibrutinib (PBS item number 11419B) of \$11,672.21. Any inconsistency may be due to rounding errors.

Source: Tables 4.5, 4.15, 4.17, pp 117, 118, 130 of the submission; Financial Worksheet '5. Impact – net'.

The redacted values correspond to the following ranges:

¹ < 500

² 500 to < 5,000

³ \$0 to < \$10 million

⁴ \$10 million to < \$20 million

6.77 The total net cost to the PBS/RPBS of listing zanubrutinib was estimated to be \$0 to < \$10 million in Year 1, increasing to \$0 to < \$10 million in Year 6, and a total of \$0 to < \$10 million over six years (as per the latest DPMQ). This increase was due to the additional seven patients with previous atrial fibrillation (4.39%) and contraindication for ibrutinib, and approximately 50% of these patients (roughly 3 patients) were estimated to receive zanubrutinib every year.

6.78 The PBAC considered it is reasonable to include newly eligible patients at risk of atrial fibrillation in the estimated PBS usage of zanubrutinib. The PBAC agreed with the DUSC that minor changes should be made to the methods used to derive the utilisation and financial estimates, and the structure of the estimates model. Specifically, the PBAC advised:

- The duration of zanubrutinib treatment should be adjusted to match Study 206 (17.8 months) or be at a cost per day that is no higher than the cost per day of other BTK inhibitors recommended for listing by the PBAC for the treatment of MCL;
- Cost offsets due to AEs should not be included;
- Utilisation of ibrutinib should be based on an average growth over 2019 and 2020;
- Grandfathered patients should be included;

- The zanubrutinib market size should be increased, by applying the age-adjusted prevalence of atrial fibrillation to estimate the increase in patient numbers corresponding to patients contra-indicated for ibrutinib but otherwise eligible for zanubrutinib.

Financial Management – Risk Sharing Arrangements

6.79 The submission proposed that uncertainties regarding market growth as well as other uncertainties associated with utilisation (Table 12) be addressed through the implementation of an appropriate Risk Sharing Arrangement (RSA). The submission did not provide details of a potential RSA. The PSCR requested that the ibrutinib RSA caps be increased to account for the small number of additional patients who would not receive ibrutinib due to the risk of atrial fibrillation but may elect treatment with zanubrutinib due to the difference in AE profiles. The PBAC considered it would be appropriate for zanubrutinib to join the existing RSA without any revision to the expenditure caps. The PBAC noted its previous concern that the prevalent patient population informing the ibrutinib estimates were potentially overestimated (paragraph 12.4, ibrutinib PSD, March 2018), and considered it would not be appropriate to revise the RSA caps without review of the actual utilisation for ibrutinib versus that expected.

Quality Use of Medicines

6.80 The PSCR stated that a Risk Management Plan (RMP) will be in place covering both WM and MCL indications for zanubrutinib, as a requirement of the TGA registration. This will include routine pharmacovigilance activities (adverse reactions reporting and signal detection) and risk minimisation activities (use of PI, CMI, packaging and medicine scheduling). The PSCR also stated that health care professionals will be supported with educational materials that address the disease, diagnosis, and treatment options, to ensure correct prescribing and appropriate patient management.

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

7 PBAC Outcome

- 7.1 The PBAC recommended the Authority Required (immediate assessment) listing of zanubrutinib for the treatment of patients with relapsed or refractory (R/R) mantle cell lymphoma (MCL) who have received at least one prior therapy and have a WHO performance status of 0 or 1. Listing was recommended on a cost-minimisation basis against ibrutinib.
- 7.2 The PBAC considered that the equi-effective doses are zanubrutinib 320 mg (four 80 mg capsules) taken orally once daily or 160 mg (two 80 mg capsules) twice daily being equivalent to ibrutinib 560 mg once daily, and advised that after adjustment for equi-effective doses, zanubrutinib should be listed on the PBS at a cost per day that is

no higher than the cost per day of other BTK inhibitors recommended for listing by the PBAC for the treatment of MCL.

- 7.3 The PBAC considered that a clinical need exists for alternative treatments in the proposed patient population because the existing option (ibrutinib) is associated with side effects. The PBAC noted the consumer comments received for this submission from health care professionals, which emphasised that zanubrutinib provides a meaningful response in patients, combined with better tolerability compared to the alternative BTK inhibitor, ibrutinib. The PBAC also noted the advice received from Lymphoma Australia, the Leukaemia Foundation, and Rare Cancers Australia which supported the proposed listing for zanubrutinib and was consistent with the evidence presented in the submission. The consumer comments from these organisations were not differentiated from those provided for acalabrutinib in R/R MCL.
- 7.4 The PBAC considered that the primary intent of the restriction should be to list zanubrutinib (i) for BTK inhibitor-naïve patients, or (ii) in patients who have developed an intolerance to another BTK inhibitor necessitating permanent treatment withdrawal. The PBAC advised that analogous criteria should flow on to the restriction for ibrutinib in MCL (item number 11419B). The PBAC advised that grandfathering would be required for < 500 patients receiving zanubrutinib under a patient access program.
- 7.5 In terms of the clinical place for zanubrutinib, the PBAC agreed with the submission that zanubrutinib will be used as an alternative to ibrutinib and will be an option for patients contra-indicated or intolerant to ibrutinib.
- 7.6 The PBAC considered that the nomination of ibrutinib as the comparator was appropriate. The PBAC noted that while immunochemotherapy may also be considered a comparator, Section 101(3B) of the National Health Act 1953 is satisfied because the PBAC has previously accepted that ibrutinib is superior to immunochemotherapy, and therefore it is also likely that zanubrutinib is superior to immunochemotherapy. The PBAC considered acalabrutinib a relevant near-market comparator.
- 7.7 The submission was based on two phase II, single-arm, open-label studies of zanubrutinib (Study 206 [N=86] and Study AU-003 [N=37]); one randomised, open-label, phase III trial comparing ibrutinib versus temsirolimus (MCL-3001/RAY [N= 139, ibrutinib arm]); and three phase II, single-arm, open-label studies of ibrutinib (PCYC-1104 [N=111], MCL-2001/SPARK [N=120] and MCL-2002 [N=16]). An additional head-to-head phase III trial of zanubrutinib versus ibrutinib (ASPEN) in another indication (WM) was used to inform the safety claim. The submission reported an analysis of the whole zanubrutinib trial populations, as well as a matching adjusted indirect comparison (MAIC) of pooled zanubrutinib and ibrutinib studies. The submission presented whole trial (naïve) and MAIC analyses for ORR, CR, PFS and OS.
- 7.8 The PBAC acknowledged that the naïve comparison between zanubrutinib and ibrutinib was uncertain, due to single arm data for both agents having differences in

study populations and durations of follow-up. The PBAC also acknowledged the uncertainty associated with the unanchored MAIC that generated a small sample size. Notwithstanding, the PBAC considered that both the naïve comparison and the MAIC analysis were consistent with non-inferiority and that on balance, zanubrutinib is likely to have similar effectiveness to ibrutinib in R/R MCL.

- 7.9 The PBAC considered the claim that zanubrutinib is superior in terms of comparative safety compared with ibrutinib was not adequately supported. The PBAC acknowledged the data in indications other than MCL suggested that treatment with zanubrutinib may be associated with a lower rate of AEs compared with ibrutinib, including lower rates of atrial fibrillation and hypertension, however based on the limited single arm data currently available for zanubrutinib in MCL, the PBAC did not accept the superiority claim.
- 7.10 The PBAC considered that the CMA should be based on the equi-effective doses of zanubrutinib and ibrutinib without including cost offsets for a reduction in AEs (proposed in a secondary economic analysis). While the PBAC agreed with the ESC that equal duration of treatment for zanubrutinib and ibrutinib was not adequately supported, the PBAC considered that the follow-up in the zanubrutinib trial was too short (median of approximately 19 months versus 39 months for ibrutinib) to provide a reliable and comparable estimate of the likely treatment duration for zanubrutinib. The PBAC therefore recommended that, after adjustment for equi-effective doses, zanubrutinib should be listed on the PBS at a cost per day that is no higher than the cost per day of other BTK inhibitors recommended for listing by the PBAC for the treatment of MCL.
- 7.11 The PBAC considered the projected utilisation to be underestimated overall, however the financial impact to the Commonwealth will be limited because the effective price for zanubrutinib derived from the CMA reflects a price that will be cost neutral when ibrutinib is substituted. The PBAC noted the listing of zanubrutinib is likely to increase the R/R MCL market size, as MCL patients with atrial fibrillation contraindicated to ibrutinib may be prescribed zanubrutinib. The PBAC advised that minor changes to the financial estimates calculation should include a duration of treatment to match Study 206 and grandfathered patients. The PBAC noted that cost offsets due to AEs should not be included, and growth in the market should be estimated from ibrutinib utilisation data using an average over 2019 and 2020. The PBAC considered it would be appropriate for zanubrutinib to join the existing RSA for ibrutinib in MCL without any revision to the expenditure caps.
- 7.12 The PBAC considered the projected utilisation to be underestimated overall, however the financial impact to the Commonwealth will be limited because the effective price for zanubrutinib derived from the CMA reflects a price that will be cost neutral when ibrutinib is substituted.
- 7.13 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because zanubrutinib is not expected to provide a substantial and

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clinically relevant improvement in efficacy, or reduction of toxicity, over ibrutinib, or not expected to address a high and urgent unmet clinical need given the presence of an alternative therapy, the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2009* for Pricing Pathway A were not met.

- 7.14 The PBAC advised that zanubrutinib is not suitable for prescribing by nurse practitioners. The PBAC noted that ibrutinib is not available for nurse prescribing.
- 7.15 The PBAC recommended that the Early Supply Rule should apply to zanubrutinib. The PBAC noted that the Early Supply Rule applies to ibrutinib.
- 7.16 The PBAC recommended that zanubrutinib should not be treated as interchangeable with any other drugs.
- 7.17 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:

Recommended

8 Recommended listing

8.1 Add new item:

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
ZANUBRUTINIB					
zanubrutinib 80 mg capsule, 120	NEW	1	120	5	Brukinsa
Restriction Summary [New 1] / Treatment of Concept [New 2]:					
Category / Program: GENERAL – General Schedule (Code GE)					
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners					
Restriction type: <input checked="" type="checkbox"/> Authority Required – immediate/real-time assessment (online/telephone)					
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.					
Administrative Advice: Special Pricing Arrangements apply.					
Administrative Advice: For the purposes of administering this restriction, current Bruton tyrosine kinase inhibitors are: acalabrutinib [pending July 2021 PBAC outcome], ibrutinib, zanubrutinib.					
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.					
Indication: Mantle cell lymphoma					
Treatment Phase: Initial treatment					
Clinical criteria:					
The condition must have relapsed or be refractory to at least one prior therapy.					
AND					
Clinical criteria:					

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	Patient must have a WHO performance status of 0 or 1.
	AND
	Clinical criteria:
	The treatment must be the sole PBS-subsidised therapy for this condition.
	AND
	Clinical criteria:
	Patient must be untreated with Bruton tyrosine kinase inhibitor therapy; or
	Patient must have developed intolerance to another Bruton tyrosine kinase inhibitor of a severity necessitating permanent treatment withdrawal, when treated for this PBS indication.
Restriction Summary [New 3] / ToC [New 4]:	
	Indication: Mantle cell lymphoma
	Treatment Phase: Continuing treatment
	Clinical criteria:
	The treatment must be the sole PBS-subsidised therapy for this condition.
	AND
	Clinical criteria:
	Patient must have previously received PBS-subsidised treatment with this drug for this condition.
	AND
	Clinical criteria:
	Patient must not have developed disease progression while being treated with this drug for this condition.
Restriction Summary [New 5] / ToC [New 6]:	
	Indication: Mantle cell lymphoma
	Treatment Phase: Transitioning from non-PBS to PBS-subsidised supply – 'Grandfather' arrangements
	Clinical criteria:
	Patient must have received treatment with this drug prior to [insert listing date here].
	AND
	Clinical criteria:
	The condition must have relapsed or be refractory to at least one prior therapy prior to initiating non-PBS-subsidised treatment with this drug for this condition.
	AND
	Clinical criteria:
	Patient must have had a WHO performance status of 0 or 1 at the time non-PBS-subsidised treatment with this drug for this condition was initiated.
	AND
	Clinical criteria:
	The treatment must be the sole PBS-subsidised therapy for this condition.
	AND
	Clinical criteria:
	Patient must have been untreated with Bruton tyrosine kinase inhibitor therapy at treatment initiation with this drug; or
	Patient must have developed intolerance to another Bruton tyrosine kinase inhibitor of a severity necessitating permanent treatment withdrawal, when treated for this PBS indication.
	AND
	Clinical criteria:
	Patient must not have developed disease progression while being treated with this drug for this condition.
	Administrative advice:
	Patients may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a 'Grandfathered' patient must qualify under the 'Continuing treatment' criteria.
	Administrative advice:
	This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria.

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8.2 Flow on changes to ibrutinib’s current Mantle cell lymphoma restrictions to permit ibrutinib use following zanubrutinib intolerance, are summarised as follows:

	MEDICINAL PRODUCT / medicinal product pack: IBRUTINIB / ibrutinib 140 mg capsule, 120
	PBS item code: 11419B
	Restriction summary: 10834 (<i>current as at 1 July 2021; only relevant edits shown below</i>) - update to form New 1
	Indication: 21449 – Mantle cell lymphoma
	Treatment phase: Initial treatment
	Clinical criteria:
	Patient must not have previously received PBS-subsidised treatment with this drug for this condition
	<i>Patient must be untreated with Bruton tyrosine kinase inhibitor therapy; or</i>
	<i>Patient must have developed intolerance to another Bruton tyrosine kinase inhibitor of a severity necessitating permanent treatment withdrawal, when treated for this PBS indication.</i>
	Administrative Advice: <i>For the purposes of administering this restriction, current Bruton tyrosine kinase inhibitors are: acalabrutinib [pending July 2021 PBAC outcome], ibrutinib, zanubrutinib.</i>
	Restriction summary: 10898 (<i>current as at 1 July 2021; only relevant edits shown below</i>) – update to form New 3
	Treatment Phase: Continuing treatment
	Clinical criteria:
	Patient must not develop disease progression while receiving PBS-subsidised treatment with this drug for this condition
	Patient must not have developed disease progression while being treated with this drug for this condition.

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

9 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.

10 Sponsor’s Comment

The sponsor had no comment.