

## 7.16 VENETOCLAX

### Tablet 10 mg, 50 mg and 100 mg, Venclexta<sup>®</sup>, AbbVie Pty Ltd.

#### 1 Purpose of Application

- 1.1 The minor resubmission sought a number of clarifications and revisions to the basis of the PBAC's July 2017 recommendation for venetoclax, as well as presenting a cost-minimisation analysis against idelalisib with rituximab and revised financial estimates for PBAC consideration.
- 1.2 Many of the issues raised by the submission regarding the basis of the PBAC's July recommendation have been addressed by the Committee outside the usual PBAC processes (see Appendix 1). These minutes record the outcomes of the PBAC's considerations in relation to the cost analysis against idelalisib and rituximab and the financial estimates presented in the minor resubmission and revised in the pre-PBAC response.
- 1.3 These minutes also record the outcomes of the PBAC's consideration of the requests, made as part of the pre-PBAC response, that PBAC give consideration to using a comparison against best supportive care (BSC) rather than idelalisib with rituximab as a basis for recommending the listing of venetoclax monotherapy, and that a Managed Access Program be developed to manage any residual uncertainty PBAC has with respect to venetoclax monotherapy.

#### 2 Background

- 2.1 Venetoclax is TGA registered for the treatment of:
  - patients with relapsed or refractory chronic lymphocytic leukaemia (R/R CLL) with 17p-deletion
  - patients with R/R CLL for whom there are no other suitable treatment options.
- 2.2 The PBAC deferred its decision in regards to venetoclax for R/R CLL in March 2017 (major submission) based on uncertainties about the appropriate comparator, relative clinical place, comparative effectiveness and safety, and duration of therapy of venetoclax against idelalisib and ibrutinib, and considered that these uncertainties flowed on to the economic evaluations and financial analyses.
- 2.3 The July 2017 PBAC meeting recommended the listing of venetoclax, on a cost-minimisation basis with idelalisib in combination with rituximab for the treatment of R/R CLL in patients who have failed a kinase inhibitor, without necessarily requiring evidence that these patients have a 17p deletion on the basis that the clinical place of venetoclax would be as a third-line treatment option for patients with R/R CLL, following treatment failure with a kinase inhibitor.

- 2.4 Subsequent to the July meeting, the PBAC provided additional advice to the Chair on a number of matters and that advice was communicated to the sponsor (see Appendix 1).

### **3 Current situation**

- 3.1 The outstanding issues raised in the minor resubmission included some of the inputs into the cost comparison analysis of venetoclax versus idelalisib with rituximab and the financial analyses.
- 3.2 The pre-PBAC response also requested that PBAC give consideration to i) using a comparison against BSC rather than idelalisib with rituximab as a basis for recommending the listing of venetoclax monotherapy, and ii) cooperatively developing a Managed Access Program to manage any residual uncertainty PBAC has with respect to venetoclax monotherapy.

### **4 PBAC considerations**

#### ***Sponsor hearing***

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

#### ***Consumer comments***

- 4.2 The PBAC noted and welcomed the input from Lymphoma Australia via the Consumer Comments facility on the PBS website, detailing some of the benefits, including the extension of life and improvement in quality of life that could be expected from listing of venetoclax for the treatment of CLL.

#### ***Economic analysis***

- 4.3 The previous submission considered by PBAC in July 2017 presented a cost-minimisation analysis against ibrutinib. The PBAC recommended venetoclax for listing on a cost-minimisation basis with idelalisib in combination with rituximab.
- 4.4 The minor resubmission presented a cost comparison analysis against idelalisib in combination with rituximab. This analysis was reviewed by the Secretariat during the evaluation of the minor submission and the resulting revised analysis was provided to AbbVie for comment as part of the pre-PBAC process.
- 4.5 The PBAC noted that the revised cost-comparison incorporated the effective price of idelalisib and that a number of fees and mark-ups had been adjusted to account for this.
- 4.6 The PBAC provided the following advice in relation to outstanding issues in the revised cost comparison analysis:
- The assumed duration of treatment with idelalisib should be 21.6 months. The assumed duration of treatment with venetoclax should be 24 months. This is

consistent with PBAC's advice in July 2017 (paragraph 7.6 of July 2017 public summary document).

- It is appropriate that the cost of prophylaxis for *Pneumocystis jirovecii* pneumonia (PJP) and monitoring for cytomegalovirus (CMV) be included in the cost of treatment for idelalisib with rituximab but not venetoclax. The PBAC noted that, in the secretariat's revised cost comparison, these costs add \$3,337 to the cost of a course of treatment with idelalisib with rituximab.
  - The DPMQ, currently \$93.55, for an authority prescription for one month's supply of 270 tablets of trimethoprim with sulfamethoxazole (TMP/SMX) for prophylaxis against (PJP), should be used in the cost comparison. The sponsor's calculations based on the DPMQ for 30 tablets resulted in overestimating the cost of TMP/SMX prophylaxis.
  - It is appropriate for the costs associated with monitoring and managing tumour lysis syndrome (TLS) to be included in the cost of a course of treatment with venetoclax. The PBAC noted that the cost comparison currently only included costs for monitoring TLS.
- 4.7 A summary of the cost comparison incorporating the changes above with the exception of the cost for managing TLS, is given in Table 1.
- 4.8 The PBAC noted that there may need to be further revisions to the cost comparison analysis during pricing negotiations to reflect usual pricing practice for cost-minimisation calculations.

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**Table 1: SUMMARY: Venetoclax effective prices based on cost comparison to idelalisib/rituximab effective price**

Drug	Form and strength	MoA	Effective AEMP	Effective DPMQ	Days of treatment per pack	Packs/infusions per 24 months	Cost per drug per course	Cost of additional prophylaxis	Cost of injection	Cost per treatment course
Idelalisib only	Tablet 150 mg	Oral	██████	██████	30	21.6	██████	\$3,337	NA	██████
Rituximab only		IV	Per PBS schedule	\$3,872.47	NA	7.8	\$29,371	NA	\$762	\$30,133
Idelalisib+rituximab	NA	NA	NA	NA	NA	NA	██████	\$3,337	\$762	██████
Venetoclax maintenance pack	Tablet 100 mg	Oral	██████	██████	30	23	██████	██████	NA	██████
Venetoclax titration (Starter pack)	Multiple	Oral	██████	██████	28	1				
Venetoclax dose hold (14 x 10 mg)	Tablet 10 mg	Oral	██████	██████	7	3.00%				
Venetoclax dose hold (7 x 50 mg)	Tablet 50 mg	Oral	██████	██████	7	3.00%				
								Net cost		██████

Source: Spreadsheet7.16 v3 VTX Cost comparison vs idela+R department.xlsx

**Estimated PBS usage & financial implications**

4.9 In its July 2017 considerations, the PBAC noted the financial estimates presented in the submission would need further negotiation between the Department and the sponsor to reflect the revised population in whom listing was recommended. The PBAC further advised that it did not expect that the costs of listing venetoclax would add greatly to the estimated costs to the PBS of listing idelalisib.

4.10 The number of venetoclax patients in the third-line population as estimated in the minor resubmission, and revised in the pre-PBAC response, are included in Table 2.

**Table 2: Number of patients expected to access venetoclax through the PBS**

	Year 1 2018	Year 2 2019	Year 3 2020	Year 4 2021	Year 5 2022	Year 6 2023	Total over 6 years of PBS listing
Minor resubmission							
Total 'highly refractory / salvage population' (third-line+)	█	█	█	█	█	█	█
Initiating patients	█	█	█	█	█	█	█
Pre-PBAC response							
Total patients	+ █ grandfather	█	█	█	█	█	+ █ grandfather
Initiating patients	+ █ grandfather	█	█	█	█	█	+ █ grandfather

Source: adapted from sponsor spreadsheet: Financial implications August minor 2017sequencing FINAL, and pre-PBAC response

4.11 The PBAC noted that the pre-PBAC response estimated the cost of listing venetoclax at the revised patient numbers (█ initiating each year) and a DPMQ of \$█ for the maintenance pack (as opposed to the sponsors proposed cost-minimisation effective DPMQ of \$█) would be more than \$100 million over 6 years before offsets for reduced use of other drugs, and more than \$100 million net over 6 years. The PBAC considered that, although these estimates had not been subject to detailed evaluation, they applied a higher price than is justified on the basis of the cost-minimisation against idelalisib and rituximab. This led to the cost of listing being overestimated.

4.12 The PBAC considered the patient numbers for the third-line population put forward with the minor resubmission had been appropriately derived and were consistent with the intent of its original recommendation for venetoclax. The PBAC considered that the subsequent revisions made to these patient numbers in the pre-PBAC response were implausible and not supported.

4.13 The PBAC noted the approximate financial impact of listing venetoclax for monotherapy based on the price presented in Table 1 and the patient estimates accepted by the PBAC, is as shown in Table 3. The PBAC noted that these estimates assume all patients start treatment on day 1 of each year and that the cost of listing venetoclax would be reduced when this assumption is adjusted to spread initiations throughout each year.

4.14 The PBAC reiterated its advice from July 2017 that a Risk Sharing Arrangement was required to be negotiated with the Department.

**Table 3: Estimated cost to the PBS of listing venetoclax**

	2018	2019	2020	2021	2022	2023	Total
Initiating patients	█	█	█	█	█	█	
Continuing patients	█	█	█	█	█	█	
Venetoclax cost to PBS (continuing patients * cost per course V/2 <sup>1</sup> )	█	█	█	█	█	█	█
Cost offsets rituximab <sup>2</sup> (initial patients* cost per course R)	█	█	█	█	█	█	█
Cost offsets idelalisib based on cap <sup>3</sup>	█	█	█	█	█	█	█
Total cost offsets	█	█	█	█	█	█	█
<b>Venetoclax net cost to PBS</b>	<b>-\$ █</b>	<b>\$ █</b>	<b>\$ █</b>	<b>\$ █</b>	<b>\$ █</b>	<b>\$ █</b>	<b>\$ █</b>

<sup>1</sup> cost of a course of venetoclax from Table 1. All patients assumed to initiate treatment on day 1 of year 1 and continue treatment for 24 months. Co-payments not accounted for.

<sup>2</sup> Assumes venetoclax will entirely replace idelalisib + rituximab in these patients.

<sup>3</sup> Year 6 Idelalisib cap assumed to be the same as Year 5 cap.

The redacted table shows that at year 5, the estimated number of patients was less than 10,000 per year.

## 5 PBAC outcome

- 5.1 The PBAC reaffirmed its July 2017 recommendation that venetoclax be subsidised through the PBS for the treatment of relapsed or refractory chronic lymphocytic leukaemia in patients who have failed a kinase inhibitor, without necessarily requiring evidence that these patients have a 17p deletion. The PBAC recommended that venetoclax be listed as Authority Required (in writing) for initial treatment and as Authority Required (telephone) for continuing treatment.
- 5.2 The PBAC recalled that it had recommended venetoclax in July 2017 on the basis of limited evidence in order to facilitate early patient access to this medicine.
- 5.3 The PBAC noted that the sponsor’s pre-PBAC response had requested that the Committee consider using a comparison against best supportive care (BSC) rather than idelalisib with rituximab as a basis for recommending the listing of venetoclax monotherapy, and that a Managed Access Program be developed to manage any residual uncertainty the PBAC has with respect to venetoclax monotherapy. The PBAC noted that a Managed Access Program would only be appropriate “where the PBAC is satisfied that new evidence will become available with a reasonable time frame that will resolve the issues of clinical and/or economic uncertainty...<sup>1</sup>”. The PBAC noted the sponsor’s advice that no more clinical data will be available for

<sup>1</sup> [www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/pbac-outcomes/2015-03/march-2015-other-matters-managed-access-programme-framework](http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/pbac-outcomes/2015-03/march-2015-other-matters-managed-access-programme-framework)

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venetoclax monotherapy, thus the requirements for a Managed Access Program cannot be met.

**Outcome:**

Recommended

**6 Recommended listing**

6.1 Add new item:

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name	Manufacturer
VENETOCLAX Tablets, 10 mg, 14, 50 mg, 7, 100 mg, 21	1	0	Venclexta®	AbbVie Pty Ltd.

<b>Category / Program</b>	GENERAL – General Schedule (Code GE)
<b>Prescriber type:</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>Severity:</b>	Relapsed or refractory
<b>Condition:</b>	Chronic lymphocytic leukaemia
<b>PBS Indication:</b>	Relapsed or refractory chronic lymphocytic leukaemia
<b>Treatment phase:</b>	Initial treatment
<b>Restriction Level / Method:</b>	<input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
<b>Clinical criteria (see section on sequencing for further information):</b>	The treatment must be as monotherapy  AND  Patient must not have previously received PBS-subsidised treatment with this drug for this condition.  AND  The condition must have relapsed or be refractory to at least a line of treatment with a kinase inhibitor.
<b>Prescriber Instructions</b>	The authority application must be made in writing and must include: a) A completed authority prescription form; b) A completed CLL PBS Authority Application – Supporting information form;

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<b>Administrative Advice</b>	<p>Any queries concerning the arrangements to prescribe may be direct to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).</p> <p>Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at <a href="http://www.humanservices.gov.au">www.humanservices.gov.au</a></p> <p>Applications for authority to prescribe should be forwarded to: Department of Human Services Complex Drugs Reply Paid 9826 HOBART TAS 7001</p> <p>No increase in the maximum quantity or number of units may be authorised.</p> <p>No increase in the maximum number of repeats may be authorised.</p> <p>Special Pricing Arrangements apply.</p>
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Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name	Manufacturer
VENETOCLAX Tablets, 10 mg, 14	1	0		
Tablets, 50 mg, 7	1	0	Venclexta®	AbbVie Pty Ltd.
Tablets, 100 mg, 120	1	5		

<b>Category / Program</b>	GENERAL – General Schedule (Code GE)
<b>Prescriber type:</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>Severity:</b>	Relapsed or refractory
<b>Condition:</b>	Chronic lymphocytic leukaemia
<b>PBS Indication:</b>	Relapsed or refractory chronic lymphocytic leukaemia
<b>Treatment phase:</b>	Continuing treatment
<b>Restriction Level / Method:</b>	<input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
<b>Clinical criteria:</b>	The treatment must be as monotherapy  AND  Patient must not develop progressive disease whilst receiving PBS-subsidised treatment with this drug for this condition  AND  Patient must have previously received PBS-subsidised treatment with this drug for this condition
<b>Administrative Advice</b>	No increase in the maximum quantity or number of units may be authorised.  No increase in the maximum number of repeats may be authorised.  Special Pricing Arrangements apply.

**Appendix 1: Responses to requests clarifications and revisions to the basis of the PBAC's July 2017 recommendation for venetoclax.**

Q) It would be useful for eventual reactive responses to external stakeholders to understand the rationale for the PBAC recommendation not to include BCRi unsuitable patients in the VTX listing. In this case, the patients' only option will be best supportive care.

A) *The PBAC did not consider that there is a population for which a kinase inhibitor is unsuitable. The patients identified as being unsuitable to ibrutinib due to "comorbidities (atrial fibrillation) and concomitant medications (anti-coagulants)" are not contra-indicated for idelalisib with rituximab which is also a kinase inhibitor. Both kinase inhibitors list hypersensitivity to both the active substance and the other components of the tablets as contra-indications in their respective PIs.*

Q) Is the detailed cost comparison provided to you on 15 Aug between Idela/R and VTX acceptable? Will that be managed outside of a minor submission process?

A) *The inclusion of further cost offsets is a new matter that was not addressed in the submission to the July meeting. Should you AbbVie to pursue this, the company would need to make a submission to the PBAC to seek a fresh PBAC recommendation.*

Q) Is sequencing allowed for the BCRis and explicitly not for VTX? This is a critical question for estimation of patient numbers and whether this has been factored into usage estimates for the market already?

A) *PBAC noted other published comparative evidence suggesting ibrutinib to be the preferred kinase inhibitor, and suggesting an alternative kinase inhibitor or venetoclax be used after initial kinase inhibitor failure. Sequencing will therefore be allowed as follows due to treatment failure: ibrutinib – idelalisib (with rituximab) – venetoclax; ibrutinib – venetoclax; or idelalisib (with rituximab) – venetoclax.*

Q) Is grandfathering of R/R CLL clinical trial patients agreed for the listing of BCRis and will that also apply to venetoclax?

A) *AbbVie has not previously requested a grandfathering restriction nor provided any details of the numbers of patients who may be eligible through previous access. AbbVie would need to make a separate submission requesting a grandfathering restriction stating the reasons why this is requested and detailing the number of patients for whom it would be applicable and how patients would meet the recommended restriction at the time of commencement of treatment (i.e. after failure with a kinase inhibitor).*

## **7 Context for Decision**

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

## **8 Sponsor's Comment**

AbbVie welcomes the Pharmaceutical Benefits Advisory Committee's (PBAC) decision to recommend the listing of VENCLEXTA (venetoclax) for the treatment of relapsed or refractory chronic lymphocytic leukemia (CLL) in patients who have failed a kinase inhibitor.

AbbVie does not agree with PBAC's assessment that venetoclax was likely to be similar in terms of effectiveness to idelalisib with rituximab in patients who have failed a kinase inhibitor and will continue to work on ensuring provision of access to patients in this area of high unmet need.