

4.06 VENETOCLAX

Tablet 10 mg, 50 mg and 100 mg, Venclexta[®], AbbVie Pty Ltd.

1 Purpose of Application

- 1.1 The minor resubmission requested a Section 85 Authority Required PBS listing for venetoclax for the treatment of relapsed or refractory chronic lymphocytic leukaemia (CLL) in patients with 17p deletion and patients with highly refractory disease.

2 Requested listing

- 2.1 The resubmission requested the following new PBS listing, the Secretariat suggestions and additions are in italics and in strikethrough for deletions.

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Published (Effective) DPMQ	Proprietary Name	Manufacturer
VENETOCLAX					
Tablets, titration pack (10 mg × 14, 50 mg × 7, 100 mg × 21)	1	0	(\$ [REDACTED])		
Tablets, 10 mg dose hold pack (10 mg × 14)	1	0	(\$ [REDACTED])	Venclexta [®]	AbbVie Pty Ltd.
Tablets, 50 mg dose hold pack (50 mg × 7)	1	0	(\$ [REDACTED])		
Tablets, maintenance pack (100 mg × 120)	1	5	(\$ [REDACTED])		

Second-line treatment:

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Severity:	<i>Relapsed or refractory</i>
Condition:	Chronic lymphocytic leukaemia
PBS Indication:	Relapsed or refractory chronic lymphocytic leukaemia
Treatment phase:	<i>Initial treatment</i>
Restriction Level / Method:	<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
Clinical criteria:	<p>The condition must have relapsed or be refractory to at least one prior therapy</p> <p>AND</p> <p><i>The treatment must be as monotherapy</i></p> <p>AND</p> <p>The patient must have <i>evidence of one or more 17p chromosomal deletions as demonstrated by fluorescence in situ hybridisation (FISH)</i></p> <p>OR</p> <p>The condition is considered highly refractory due to the following:</p> <p>— Relapsed/refractory to at least two prior lines of therapy including at least one line of chemoimmunotherapy; AND</p> <p>— Intolerant to or inadequately responsive to B-cell receptor signal inhibitors [on the assumption that at least one B-cell receptor signal inhibitor is PBS-listed].</p> <p>If the patient cannot be treated with a B-cell receptor signal inhibitor (BCRi), or two prior lines of therapy because of contraindications according to the relevant TGA approved Product Information and/or intolerances of a severity necessitating permanent treatment withdrawal, details of the contraindication and/or intolerance must be provided in the Authority application.</p> <p>AND</p> <p><i>Patient must not have previously received PBS-subsidised treatment with this drug for this condition.</i></p> <p>AND</p> <p><i>Patient must not have previously received PBS-subsidised treatment with ibrutinib or idelalisib for this condition</i></p>
Administrative Advice	<i>Special Pricing Arrangements apply.</i>

Third-line treatment:

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Severity:	Relapsed or refractory
Condition:	Chronic lymphocytic leukaemia
PBS Indication:	Relapsed or refractory chronic lymphocytic leukaemia
Treatment phase:	Initial treatment
Restriction Level / Method:	<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
Clinical criteria:	<i>The condition must have relapsed or be refractory to at least two prior therapies which must include a line of treatment with a B-cell receptor signal inhibitor.</i> AND <i>The treatment must be as monotherapy</i> AND <i>Patient must not have previously received PBS-subsidised treatment with this drug for this condition.</i>
Administrative Advice	<i>Special Pricing Arrangements apply.</i>

Second- and third-line treatment – continuing treatment:

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Severity:	Relapsed or refractory
Condition:	Chronic lymphocytic leukaemia
PBS Indication:	Relapsed or refractory chronic lymphocytic leukaemia
Treatment phase:	Continuing treatment
Restriction Level / Method:	<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
Clinical criteria:	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
Administrative Advice	Special Pricing Arrangements apply.

For more detail on PBAC’s view, see section 7 “PBAC outcome.”

3 Background

- 3.1 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.
- 3.2 The approved TGA indication notes “the indications are based on overall response rates. Duration of response and improvements in overall survival, progression-free survival or health-related quality of life have not been established”.
- 3.3 The PBAC deferred its decision in regards to venetoclax of relapsed or refractory 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.

- 3.4 The current minor resubmission sought to address the outstanding issues of the choice of comparator, cost minimisation against the comparator and overall cost to government through willingness to enter negotiations for a Risk Sharing Arrangement (RSA).
- 3.5 Table 1 summarises the key differences between the March 2017 submission and the July 2017 minor resubmission. Table 2 provides further details on the comparison across the comparator drugs for the treatment of CLL.

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Table 1. Summary of the differences between the previous venetoclax submission and current resubmission

	March 2017 submission	Current resubmission
Requested PBS listing	For the treatment of relapsed or refractory chronic lymphocytic leukaemia (CLL) in patients with 17p deletion/TP53 mutation and patients with highly refractory disease.	For the treatment of relapsed or refractory chronic lymphocytic leukaemia (CLL) in patients with 17p deletion mutation and patients with highly refractory disease.
Requested effective DPMQs	<p>Initial treatment: titration pack 14 x 10 mg tablets; 7 x 50 mg tablets; 7 x 100 mg tablets; 14 x 100 mg tablets</p> <ul style="list-style-type: none"> • \$ [REDACTED] (Published) • \$ [REDACTED] (Effective) <p>Dose hold packs 14 x 10 mg</p> <ul style="list-style-type: none"> • \$ [REDACTED] (Published) • \$ [REDACTED] (Effective) <p>7 x 50 mg</p> <ul style="list-style-type: none"> • \$ [REDACTED] (Published) • \$ [REDACTED] (Effective) <p>Continuing treatment 120 x 100 mg</p> <ul style="list-style-type: none"> • \$ [REDACTED] (Published) • \$ [REDACTED] (Effective) 	<p>Same as the cost-minimisation approach against ibrutinib in the previous pre-PBAC response, with an acknowledgement that this will require adjustment to account for the effective price of ibrutinib.</p> <p>Cost of tumour lysis syndrome (TLS) prophylaxis monitoring off-set: \$ [REDACTED]</p>

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	March 2017 submission	Current resubmission
Comparator	<p>Ofatumumab monotherapy as the main comparator in patients with 17p deletion/TP53 mutation, Rituximab monotherapy (as a proxy for best supportive care) as the main comparator in patients with highly refractory disease.</p> <p>PBAC comment: (PSD paragraph 5.3) The PBAC has previously accepted that survival outcomes for rituximab monotherapy (but not costs or treatment-related utilities) may be a proxy for best supportive care given the absence of evidence supporting a survival benefit for rituximab monotherapy. (paragraph 7.4) The PBAC considered that the submission's nomination of ofatumumab as the most relevant comparator, and the consequential clinical, economic and financial assessments involving this comparator, were not informative. The Committee noted that the pre-PBAC response agreed that idelalisib and ibrutinib were the most relevant comparators, and presented a cost-minimisation analysis against ibrutinib. Given the uncertainty about the relative clinical place of venetoclax against idelalisib and ibrutinib, the PBAC considered that the appropriate comparator remained unclear.</p>	<p>Ibrutinib in relapsed or refractory CLL patients with a 17p deletion. Claim that idelalisib with rituximab is not an appropriate comparator as "it is very unlikely that clinicians would pursue treatment with idelalisib with rituximab if venetoclax and/or ibrutinib were listed on the PBS."</p> <p>Unchanged for highly refractory disease.</p>

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	March 2017 submission	Current resubmission
Clinical evidence	<p>A series of naïve indirect comparisons:</p> <ul style="list-style-type: none"> • venetoclax (M12-175, M13-982) versus ofatumumab monotherapy (RESONATE) for patients with a 17p deletion/TP53 mutation; • venetoclax (M12-175, M13-982) versus idelalisib with rituximab (312-0116) for patients with a 17p deletion/TP53 mutation; • venetoclax (M12-175, M13-982) versus ibrutinib (RESONATE, RESONATE-17) for patients with a 17p deletion/TP53 mutation; • venetoclax (M14-032) versus rituximab monotherapy (312-0116) for patients with no other suitable treatment options. <p>PBAC comment: (PSD paragraph 7.5) The PBAC considered that the clinical data available were less robust than would typically be relied on for decision making across all the subgroups requested, with no randomised trials reported, insufficient follow-up of more patient relevant outcomes such as overall survival, and evidence of observer bias (investigator assessed response rates were more favourable than independent committee response rates). In particular, the PBAC noted that the data for venetoclax to support the requested third-line listing or the TP53 mutated subgroup were less robust than the data available for the 17p deletion subgroup. However, the PBAC also recalled that the data available to inform its considerations about the listing of ibrutinib and idelalisib were not fully robust, albeit not necessarily for the same reasons.</p>	No new data presented.

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	March 2017 submission	Current resubmission																																																																								
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	March 2017 submission	Current resubmission
Clinical claim	<p>Superior in terms of comparative efficacy, with a non-inferior safety profile compared to idelalisib with rituximab in patients with relapsed or refractory CLL and a 17p deletion/TP53 mutation.</p> <p>Equivalent in efficacy and safety to ibrutinib in patients with relapsed or refractory CLL and a 17p deletion/TP53 mutation.</p> <p>Superior in terms of comparative efficacy, with inferior safety compared to rituximab monotherapy in patients with highly refractory disease.</p> <p>PBAC comment: (PSD paragraphs 6.37 and 6.38) The PBAC considered that the claims of comparative effectiveness between venetoclax and idelalisib or ibrutinib were not adequately supported by the data.</p> <p>The PBAC considered that the claims of comparative safety between venetoclax and idelalisib or ibrutinib were not adequately supported by the data.</p> <p>(paragraph 6.36) Despite the limited evidence, this claim (Superior in terms of comparative efficacy, with inferior safety compared to rituximab monotherapy in patients with highly refractory disease) may be reasonable in terms of efficacy and safety. However, the magnitude of any benefit was unclear.</p>	<p>Venetoclax is non-inferior to ibrutinib in patients with relapsed or refractory CLL and a 17p deletion in terms of both efficacy and safety. <i>See Table 3, below.</i></p> <p>Venetoclax is an effective treatment with high 12-month PFS and OS rates in patients with highly refractory disease with no other suitable treatment options. <i>See Table 4, below.</i></p>

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	March 2017 submission	Current resubmission
Economic evaluation	<p>A modelled cost-utility analysis assessing the value of venetoclax compared to ofatumumab monotherapy in patients with 17p deletion/TP53 mutation; pre-PBAC provided a CMA against ibrutinib over 27.2 months.</p> <p>A modelled cost-utility analysis assessing the value of venetoclax compared to rituximab monotherapy (proxy for best supportive care) in patients with highly refractory disease. ICER \$75,000/QALY – \$105,000/QALY.</p> <p>PBAC comment: (7.4) The PBAC considered that the submission's nomination of ofatumumab as the most relevant comparator, and the consequential clinical, economic and financial assessments involving this comparator, were not informative. The Committee noted that the pre-PBAC response agreed that idelalisib and ibrutinib were the most relevant comparators, and presented a cost-minimisation analysis against ibrutinib. Given the uncertainty about the relative clinical place of venetoclax against idelalisib and ibrutinib, the PBAC considered that the appropriate comparator remained unclear.</p>	<p>Cost-minimisation analysis against ibrutinib over 24 months treatment on the basis of 400 mg once-daily venetoclax being equi-effective to 420 mg ibrutinib once daily over 24 months and with an offset for the increased cost associated with monitoring TLS. <i>The duration of ibrutinib in the relevant trial was 22.2 months, so alternative conclusions of equi-effective doses could be (a) limited to 22.2 months for both medicines, or (b) some estimate of duration between these two observed durations.</i></p> <p>ICER in highly refractory disease \$75,000/QALY – \$105,000/QALY (updated mark-ups etc).</p>
Number of patients	<p>Less than 10,000 in year 1 increasing to less than 10,000 in year 5. The pre-PBAC response updated this to less than 10,000 462 in year 1 increasing to less than 10,000 in year 5.</p>	<p>Less than 10,000 in year 1 increasing to less than 10,000 in year 2 before decreasing to less than 10,000 in year 5. (includes a prevalent pool of eligible patients peaking in year 2).</p>
Estimated net cost to PBS	<p>The net cost to PBS of listing venetoclax on the PBS was estimated to be up to \$10 – \$20 million in the fifth year of listing based on the effective price (published price, \$10 – \$20 million). The estimated cumulative cost over five years was \$30 – \$60 million (published price, \$60 – \$100 million per year). The estimated cumulative cost to government after accounting for TLS prophylaxis and infusion costs with substituted therapies was \$30 – \$60 based on the effective price (published price, \$30 – \$60).</p> <p>The pre-PBAC response updated the financial estimates to a net cost to the PBS/RPBS of \$20 – \$30 million in year 1 rising to \$30 – \$60 million in year 5.</p> <p>PBAC comment: (paragraph 7.6) Given the uncertainty around the clinical place of venetoclax, the PBAC considered that the clinical, economic and financial assessments provided to compare venetoclax with idelalisib or ibrutinib were insufficient to form the basis of a recommendation to list venetoclax on the PBS</p>	<p>The drug cost to PBS of listing venetoclax \$30 – \$60 million year 1, \$60 – \$100 million in year 2 and then decreases in year 5 to \$30 – \$60 million. Proposed offsets for displaced therapy in the 17p deleted population (ibrutinib), brings the overall net cost to the PBS to \$10 – \$20 million in year 1 and after rising \$30 – \$60 million in year 2, decreased to \$10 – \$20 million in year 5.</p>

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	March 2017 submission	Current resubmission
Risk sharing arrangement	Not proposed, but open to enter into a risk sharing arrangement.	Not mentioned.
PBAC decision	Defer. PBAC Comment: (paragraph 7.1) The PBAC deferred making a decision regarding venetoclax for the treatment of certain patients with chronic lymphocytic leukaemia (CLL). The PBAC considered that the comparator of ofatumumab nominated in the submission was not relevant because there is no overlap in the treated populations. The PBAC instead considered ibrutinib and idelalisib to be more relevant comparators, given the PBAC’s recent considerations of these medicines in similar CLL populations. The PBAC was also particularly uncertain about the relative clinical place, comparative effectiveness and safety, and duration of therapy of venetoclax against these two alternatives, and considered that these uncertainties flowed on to the economic evaluations and financial analyses. The PBAC deferred making a decision pending further information clarifying these issues as further outlined below.	-

For more detail on PBAC’s view, see section 7 “PBAC outcome.”

4 Population and disease

- 4.1 The March 2017 submission positioned venetoclax as a second-line treatment option in patients with relapsed or refractory CLL who have a 17p deletion or TP53 mutation. That submission also positioned venetoclax as a third-line treatment option in patients with relapsed or refractory CLL without a 17p deletion or TP53 mutation. It noted that the intended place for venetoclax in this population was for patients with no other suitable treatment options.
- 4.2 The PBAC in March 2017 considered that uncertainty remained around the likely place of venetoclax in clinical practice, specifically with regard to the possibility of its use as combination therapy, whether it would be used in an earlier line of therapy than the third-line for relapsed or refractory CLL proposed in the submission, and the relative place in comparison to ibrutinib and idelalisib if they were listed on the PBS.
- 4.3 The resubmission again proposed venetoclax as a second-line treatment option in patients with relapsed or refractory CLL who have a 17p deletion. The resubmission also positioned venetoclax as a third-line treatment option in patients with highly refractory CLL without a 17p deletion.
- 4.4 The PBAC considered that, based on the clinical evidence available to it, the clinical place of venetoclax would be as a third-line treatment option in patients with relapsed or refractory CLL, following treatment failure with a kinase inhibitor.

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

5 Comparator

- 5.1 The minor resubmission nominated ibrutinib as the comparator for relapsed or refractory CLL patients with a 17p deletion. The previous submission considered by the PBAC in March 2017 nominated best supportive care for the highly refractory population. This was unchanged in this resubmission.
- 5.2 The resubmission presented an argument as to why it did not consider idelalisib with rituximab as a relevant comparator, which was based on recent safety concerns raised by the TGA for the use of this combination in some circumstances and the previously submitted clinician survey results that indicated that the majority of those surveyed would prescribe with either ibrutinib or venetoclax over idelalisib with rituximab.
- 5.3 The PBAC did not support ibrutinib as the appropriate comparator due to weak supportive data for venetoclax in this setting where ibrutinib is already more

established based on earlier evidence (see section 6 for more detail), and instead considered that a more appropriate comparator was idelalisib with rituximab in the later clinical setting following treatment failure with a kinase inhibitor.

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

6 Consideration of the evidence

Sponsor hearing

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

Consumer comments

6.2 The PBAC noted and welcomed the input from individuals (2) and organisations (2) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with venetoclax including the opportunity to extend the length and quality of life and a possible cure in CLL negating the need for a stem cell transplant (however, the PBAC considered that this last possibility of a cure was not supported by the available evidence).

6.3 The PBAC noted the support received from Lymphoma Australia and Rare Cancers Australia 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.

Clinical trials

6.4 As a minor submission, no new clinical trials were presented in the resubmission.

6.5 The basis of the minor resubmission's request was a change in the proposed comparator in the 17p deletion population to ibrutinib, which was recently recommended by the PBAC for relapsed or refractory CLL.

Comparative effectiveness

6.6 The trial results remain unchanged from the previous major submission considered in March 2017. The results from indirect comparison in the March 2017 submission for the 17p deletion population versus ibrutinib are repeated below.

Table 2. Summary of the most recent efficacy results for venetoclax vs. ibrutinib in patients with a 17p deletion

	M12-175	M13-982	RESONATE	RESONATE17
	VEN 400 mg 17p del (N = 14)	VEN main cohort (N = 158)	IBRU 17p del (N = 63)	IBRU all subjects (N = 144)
Median duration of treatment, months (range)	█ █ █	█ █ █	16 (NR) ¹	NR
Median duration of follow-up, months (range)	█	█	16 (NR) ¹	27.6 (14.6-27.7) ¹
Response rates				
Overall response rate, % (95% CI)	█ █ █ █	77.2 (69.9, 83.5)	NR	83 (76, 89) ²
- Complete response, n (%)	█	29 (18.4)	NR	15 (10)
- Partial response, n (%)	█ █ █ █	93 (58.9)	NR	105 (73) ²
Progression-free survival				
Events n (%)	█ █ █ █	█ █ █ █	NR	NR
Median PFS, months (95% CI)	█ █ █ █	27.2 (21.9, NE)	Not reached (NR) ³	Not reached (27.7, NE)
KM estimate of PFS at 6 months, % (95% CI)	█ █ █ █	█ █ █ █	NR	NR
KM estimate of PFS at 12 months, % (95% CI)	█ █ █ █	77 (69, 83)	79 (NR)	80 (NR) ⁴
Overall survival				
Deaths n (%)	█ █ █ █	40 (25.3)	NR	NR
Median OS, months (95% CI)	█ █ █ █	Not reached █ █ █	NR	Not reached (29.5, NE)
KM estimate of OS at 6 months, % (95% CI)	█ █ █ █	█ █ █ █	NR	NR
KM estimate of OS at 12 months, % (95% CI)	█ █ █ █	87 (80, 91)	NR	84 (NR) ⁴

Abbreviations: 17p del, 17 deletion subgroup; CI, confidence interval; IBRU, ibrutinib; KM, Kaplan-Meier; NE, not evaluable; NR, not reported; OS, overall survival; PFS, progression free survival; RITU, rituximab; VEN, venetoclax

¹ Interquartile range

² Includes partial response with lymphocytosis

³ Results from 9-month analysis; not reported in 16-month analysis

⁴ Based on interpolation of Kaplan-Meier data by the sponsor

Source: PBAC March 2017 minutes.

6.7 The key results of the naïve indirect comparison between venetoclax and rituximab monotherapy in patients with highly refractory disease are summarised in Table 3.

Table 3. Summary of the most recent efficacy results for venetoclax vs. rituximab monotherapy in overall study populations

	M14-032	312-0116
	VEN all subjects (N = 64)	PBO + RITU all subjects (N = 110)
Median duration of treatment, months (range)	11.7 (0.1-17.9)	4.6 (0.1-14.6)
Median duration of follow-up, months (range)	NR	11.1 (0.2-24.6)
Response rates		
Overall response rate, % (95% CI)	67.2 (54.3, 78.4)	15.5 (9.3, 23.6)
- Complete response, n (%)	1 (1.6)	0
- Partial response, n (%)	42 (65.6)	(15.5)
Progression-free survival		
Events n (%)	12 (18.8%)	(63.6)
Median PFS, months (95% CI)	Not reached (13.2, NE)	6.5 (4.0, 7.3)
KM estimate of PFS at 6 months, % (95% CI)		NR
KM estimate of PFS at 12 months, % (95% CI)	81 (68, 89)	9.2 (NR)
Overall survival		
Death n (%)		(36.4)
Median OS, months (95% CI)		20.8 (14.8, NE)
KM estimate of OS at 6 months, % (95% CI)		NR
KM estimate of OS at 12 months, % (95% CI)		67 (NR)

Abbreviations: CI, confidence interval; KM, Kaplan-Meier; NE, not evaluable; NR, not reported; OS, overall survival; PBO, placebo; PFS, progression free survival; RITU, rituximab; VEN, venetoclax

Source: March 2017 minutes

6.8 The PBAC further compared the effectiveness of venetoclax with the recently recommended therapies ibrutinib and idelalisib with rituximab as summarised in the table below.

Table 4. Summary of the most recent efficacy results for venetoclax vs. ibrutinib or idelalisib with rituximab monotherapy in overall study populations

	Venetoclax			Ibrutinib		Idelalisib
	M12-175	M13-982	M14-032	RESONATE	RESONATE-17	312-0116
	VEN 400mg cohort (N=67)	VEN all subjects (N=158)	VEN IBRU failures (N=43)	IBRU (N=195) ¹	IBRU (N=144)	IDEL + RITU (N=110)
Median duration of treatment, months (range)			12.4 (0.1-17.9)	16 (NR)	NR	8.1 (0.3-19.5)
Median duration of follow-up, months (range)			NR	16 (NR)	27.6 (14.6-27.7)	12.5 (0.3-25.1)
Response rates						
Overall response rate, % (95% CI)		77.2 (69.9, 83.5)	69.8 (53.9, 82.8)	90 (NR)	83 (76, 89)	83.6 (75.4, 90.0)
Complete response, n (%)		29 (18.4)	1 (2.3)	(6)	15 (10)	0
Partial response, n (%)		93 (58.9)	29 (67.4)	(84)	105 (73)	(83.6)
Progression free survival						
Events n/N (%)				NR	NR	(22.7)
Median PFS, months (95% CI)		27.2 (21.9, NE)		Not reached (NR)	Not reached (27.7, NE)	19.4 (12.3, NE)
KM estimate of PFS - 6 months, % (95% CI) - 12 months, % (95% CI)		 77 (69, 83)		NR 84 (NR)	NR 80 (NR) ³	NR 70 (NR)
Overall survival						
Death n/N (%)				NR	NR	(15.5)
Median OS, months (95% CI)		Not reached		Not reached (NE)	Not reached (29.5, NE)	Not reached (NE)
KM estimate of OS - 6 months, % (95% CI) - 12 months, % (95% CI)		 87 (80, 91)		NR 90 (NR)	NR 84 (NR)	NR 89 (NR)

Abbreviations: CI, confidence interval; KM, Kaplan-Meier; NE, not evaluable; NR, not reported; OS, overall survival; PBO, placebo; PFS, progression free survival; RITU, rituximab; VEN, venetoclax; IDEL, idelalisib.

¹ Complete ibrutinib arm of the RESONATE trial.

Source: Compiled during consideration.

6.9 The PBAC noted that the naïve comparisons across the venetoclax and idelalisib with rituximab studies gave numerically varying incremental results depending on whether these comparisons were based on overall response rates (complete plus partial responses), which numerically favoured idelalisib with rituximab, or on complete response rates only, which numerically favoured venetoclax. Additionally, the likely more biased investigator-assessed outcomes were generally more favourable than the likely less biased centrally-assessed outcomes for venetoclax. For example, limiting the analysis of M13-982 at the April 2015 data cut to centrally-assessed complete response rates reduced the complete response rates for venetoclax (15.9% vs. 7.5% for investigator-assessed).

Comparative harms

- 6.10 The resubmission again claimed that venetoclax has a different and likely non-inferior adverse event profile compared to ibrutinib. No new data was provided to support this claim.
- 6.11 The PBAC recalled its previous consideration of venetoclax, where treatment appeared to be associated with higher rates of cytopenias, with the following data highlighted:
- neutropenia ranged from ██████% for venetoclax compared to 16% for ibrutinib and 23% for idelalisib with rituximab;
 - anaemia ranged from ██████% for venetoclax compared to 5% for ibrutinib and 7% for idelalisib with rituximab;
 - thrombocytopenia ranged from ██████% for venetoclax compared to 6% for ibrutinib and 4% for idelalisib with rituximab;
 - deaths due to tumour lysis syndrome (TLS) were reported in Study M12-175 which resulted in the development of a TLS monitoring program.
- 6.12 The resubmission acknowledged the heightened risk of TLS following venetoclax, which requires patients to be near a hospital in the first month of treatment with a need for intense monitoring and prophylaxis.

Benefits and harms

- 6.13 In March 2017, the PBAC considered that the trial results presented were insufficient information to reliably quantify the benefits and harms of venetoclax compared to its nominated comparators (ofatumumab monotherapy, rituximab monotherapy; ibrutinib; idelalisib with rituximab).

Clinical claim

- 6.14 The resubmission claimed non-inferior comparative effectiveness and non-inferior comparative safety of venetoclax compared with ibrutinib.
- 6.15 The PBAC recalled that it had considered in March 2017 that the claims of comparative effectiveness and safety between venetoclax and idelalisib or ibrutinib were not adequately supported by the data.
- 6.16 The PBAC considered that it was not currently possible to reliably assess the claim of non-inferior comparative effectiveness to ibrutinib. Rather, the available evidence suggests that venetoclax may be clinically inferior to ibrutinib. The PBAC considered it was important that the comparative effectiveness was reliably determined given

that the cancer is relatively common and two kinase inhibitors (ibrutinib and idelalisib) have recently been recommended for PBS listing for use in this disease. The PBAC also considered that it was likely that there are potentially important differences across these therapies, and thus stronger evidence was needed to support listing of this subsequent medication as an earlier line of treatment. The PBAC considered that, in terms of effectiveness, venetoclax was likely to be non-inferior to idelalisib with rituximab after failure of a kinase inhibitor in relapsed or refractory CLL, with ibrutinib more likely to be used before either of these options.

- 6.17 The PBAC again considered that the claims of non-inferior safety between venetoclax and idelalisib with rituximab or ibrutinib were not adequately supported by the data.

Economic analysis

- 6.18 The minor resubmission presented a cost-minimisation analysis (CMA) against ibrutinib in the 17p deletion population over a 24-month treatment duration. The assumptions that form the basis for the CMA are presented in Table 5.

Table 5. Key assumptions of the cost-minimisation analysis for patients with a 17p deletion

Component	Claim or assumption
Therapeutic claim: efficacy	Based on the evidence presented in this resubmission, venetoclax is assumed to be non-inferior to ibrutinib with respect to efficacy
Therapeutic claim: safety	Based on the evidence presented in this resubmission, venetoclax is assumed to be non-inferior to ibrutinib with respect to safety
Evidence base	Naïve comparison of clinical trials
Equi-effective doses	400 mg once daily venetoclax is equi-effective to 420 mg ibrutinib once daily
Direct medicine costs	The per-patient drug cost of venetoclax is lower than the per-patient cost of ibrutinib (to offset the increased cost associated with monitoring TLS in venetoclax patients)
Other costs or cost offsets	The costs of monitoring and preventing venetoclax-induced TLS during the titration month have been included
Basis of cost-minimisation	24 months treatment duration with venetoclax is equivalent to 24 months treatment duration with ibrutinib

Abbreviations: TLS = tumour lysis syndrome

- 6.19 As a minor resubmission, the cost-minimisation analysis was not independently verified.
- 6.20 In the previous major submission considered by PBAC in March 2017, the submission presented a cost-effectiveness analysis against best supportive care for the highly refractory third-line population. The minor resubmission did not alter the economic model structure from March 2017 or the requested effective price of \$ [REDACTED] for venetoclax for this population. However, several other input costs have changed since the original submission and the resubmission sought to respecify the best estimate of the base case ICER by substituting these values, along with using the most efficient combination of rituximab vials in the initial dose, into the previously

submitted model. The resultant ICER increased from \$75,000/QALY – \$105,000/QALY in the March 2017 submission to \$75,000/QALY – \$105,000/QALY. The respecified base case ICER was not independently verified. The PBAC recalled that it had considered that the March 2017 ICER could not be relied upon due to uncertainty regarding modelled survival data (particularly treatment efficacy estimates). In addition, the PBAC considered that this economic evaluation was no longer relevant given its view that idelalisib is now the appropriate comparator in this setting rather than BSC.

- 6.21 The minor resubmission did not indicate whether the revised effective price from a fully informed cost-minimisation approach would then also be applied to this second population (which would produce a more acceptable ICER). Alternatively, the resubmission did not specify how the requested Special Pricing Arrangement would resolve having two effective prices across two populations. In its pre-PBAC response, the sponsor indicated that it was willing to accept the cost-minimised price against ibrutinib in both populations for which listing was proposed.
- 6.22 The PBAC did not support the cost-minimisation approach against ibrutinib as the Committee did not consider that venetoclax was non-inferior to ibrutinib.
- 6.23 The PBAC considered that, on the basis of the clinical studies provided, venetoclax should be cost minimised against idelalisib with rituximab on the basis that 400 mg/day venetoclax for 24 months and 300 mg/day idelalisib for [REDACTED] months with rituximab 500 mg/m² every 4 weeks for 6 months are equi-effective. The estimated durations of treatment were derived from the sponsors' modelled extrapolations from these studies, with the numerical difference in durations falling within the variation that could be expected from the quality of the evidence available for the cost-minimisation approach and a necessary consequence of needing to determine a basis for its calculation. The cost-minimisation approach should also take into consideration for venetoclax both the need for a titration pack and also an offset for the increased cost associated with monitoring and managing TLS.

Drug cost/patient/course:

- 6.24 The resubmission used the same proposed DPMQ as the March 2017 major submission to calculate the cost to the PBS below. Based on the proposed DPMQ, the cost per patient per course is presented in the table below.

Table 6. Drug cost per patient for initial and subsequent 24 weeks of treatment

Treatment regimen	Calculation	Cost per patient
Initial 24 weeks		
Venetoclax	Weeks 1-4 = \$ [REDACTED] (effective DPMQ for titration pack) Weeks 5-8 = \$ [REDACTED] (based on weighted effective DPMQ for maintenance pack, 10 mg dose hold pack, and 50 mg dose hold pack with distribution assumptions from the resubmission) ^a Weeks 9-24 = \$ [REDACTED] (calculated using effective DPMQ for maintenance pack x 112 days per 16 weeks/30 days treatment per pack)	\$ [REDACTED]
Subsequent 24 weeks		
Venetoclax	Effective DPMQ for maintenance pack x 168 days per 24 weeks/30 days treatment per pack	\$ [REDACTED]

6.25 The PBAC did not support the above price proposal and considered that the alternative cost-minimisation approach against idelalisib + rituximab was more appropriate.

Estimated PBS usage & financial implications

6.26 The minor resubmission, based on the March 2017 DPMQ, estimated a net cost to the PBS of \$10 - \$20 million in Year 1 of listing, increasing to \$30 – \$60 million in year 2 then decreasing to \$10 – \$20 million in year 5, with a total net cost to the PBS of more than \$100 million over the first 5 years of listing.

6.27 The PBAC did not consider that the patient numbers or the financial estimates proposed by the sponsor were informative based on the recommendation to list after failure of a kinase inhibitor. The PBAC considered that the use of venetoclax as recommended would substitute for idelalisib with rituximab on the PBS on a cost-minimisation basis. The PBAC considered that the financial implications of listing venetoclax would need further negotiation between the Department and the sponsor, but advised that these should not greatly add to the costs to the PBS of idelalisib.

Financial Management – Risk Sharing Arrangements

6.28 The sponsor expressed a willingness to enter into a Risk Sharing Arrangement to address the financial uncertainty associated with the PBS listing of venetoclax in its March 2017 submission.

6.29 The sponsor also requested a Special Pricing Arrangement, where the sponsor would provide a confidential rebate to the published price of venetoclax.

6.30 The PBAC considered that a Risk Sharing Arrangement was required to be negotiated with the Department to reduce the risk of use outside the specified restriction and to take into account the PBAC’s advice about the overall costs to the PBS.

For more detail on PBAC’s view, see section 7 “PBAC outcome.”

7 PBAC Outcome

- 7.1 The PBAC recommended the listing of venetoclax, on a cost-minimisation basis with idelalisib in combination with rituximab for the treatment of relapsed or refractory chronic lymphocytic leukaemia (CLL) in patients who have failed a kinase inhibitor, without necessarily requiring evidence that these patients have a 17p deletion.
- 7.2 The PBAC advised that the clinical place of venetoclax would be as a third-line treatment option for patients with relapsed or refractory CLL, following treatment failure with a kinase inhibitor. As ibrutinib is the most likely kinase inhibitor to be used for relapsed or refractory CLL, eligibility for ibrutinib on the basis of a 17p deletion would have been established before considering venetoclax, so there is no need for the venetoclax PBS restriction to include an option for determining eligibility on the basis of 17p deletion, nor for the corresponding MBS item to mention venetoclax. The reference to 17p deletion in relation to the kinase inhibitors ibrutinib and idelalisib should remain for both their PBS restrictions and the corresponding MBS item.
- 7.3 The PBAC based its advice relating to the clinical place of venetoclax on the clinical evidence available to it and the fact that the optimal sequencing of ibrutinib, idelalisib and venetoclax is still being determined. The PBAC noted other published comparative evidence suggesting ibrutinib to be the preferred kinase inhibitor, and suggesting an alternative kinase inhibitor or venetoclax to be used after initial kinase inhibitor failure.¹
- 7.4 The PBAC therefore rejected the request to list venetoclax as a second-line treatment option in patients with relapsed or refractory CLL who have a 17p deletion. The PBAC considered that, from the evidence currently available, there was an insufficient basis to justify that venetoclax could substitute for ibrutinib in this population. Based on earlier clinical evidence, ibrutinib is already more established as a therapy in relapsed or refractory CLL. This has reduced the residual unmet clinical need in relapsed or refractory CLL, thus weakening the current submission's request for the PBAC to rely on arguably similarly weak evidence for venetoclax as the next presented therapy. The PBAC remained of the view that it was impossible to reliably assess the claim of non-inferior comparative effectiveness between venetoclax and ibrutinib, and considered that this was important given the context of a relatively common cancer, where alternative therapies (ibrutinib and idelalisib) have recently been recommended for listing. The PBAC also considered that it was likely that there are potentially important differences across these therapies, and thus stronger evidence was needed to subsequently support listing of venetoclax for

¹ Mato AR et al. *Annals of Oncology* 2017; 28:1050-6.

the same earlier line of treatment.

- 7.5 The PBAC confirmed that there would remain a residual unmet clinical need for further treatment options in relapsed or refractory CLL following failure with an initial kinase inhibitor, and that the place of venetoclax treatment would be more likely to be in this other requested population as an alternative to idelalisib with rituximab. The PBAC further considered that, from the limited evidence currently available, venetoclax was likely to be clinically non-inferior to idelalisib with rituximab after failure of a kinase inhibitor in relapsed or refractory CLL.
- 7.6 The PBAC recommended that venetoclax be cost minimised against idelalisib on the basis of the clinical studies provided with sponsor-sourced modelled extrapolations of treatment duration. The PBAC advised that 400 mg/day venetoclax for 24 months and 300 mg/day idelalisib for [REDACTED] months with rituximab 500 mg/m² every 4 weeks for 6 months are equi-effective; and that the cost-minimisation should also take into consideration for venetoclax both the need for a titration pack and also an offset for the increased cost associated with monitoring and managing TLS.
- 7.7 The PBAC did not consider that the financial estimates proposed by the sponsor were informative for the recommended population. The PBAC considered that the financial implications of listing venetoclax would need further negotiation between the Department and the sponsor, but advised that these should not greatly add to the costs to the PBS of idelalisib.
- 7.8 The PBAC considered that a Risk Sharing Arrangement was required to be negotiated with the Department to reduce the risk of use outside the specified restriction and to take into account the PBAC's advice about the overall costs to the PBS.
- 7.9 The PBAC did not consider that there was sufficient data to support retreatment with venetoclax and that this was also the case for ibrutinib and idelalisib, and the following wording should be included in the initial restriction for all three of these medicines: "Patient must not have previously received PBS-subsidised treatment with this drug for this condition."
- 7.10 The PBAC advised that venetoclax is not suitable for prescribing by nurse practitioners.
- 7.11 The PBAC recommended that venetoclax should not be treated as interchangeable on an individual patient basis with any other drugs, particularly noting the different mechanism of action of venetoclax to other available drugs.
- 7.12 The PBAC recommended that the Early Supply Rule should apply.

7.13 The PBAC noted that this submission was not eligible for an Independent Review as it was a positive recommendation.

Outcome:

Recommended

8 Recommended listing

8.1 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.

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Severity:	Relapsed or refractory
Condition:	Chronic lymphocytic leukaemia
PBS Indication:	Relapsed or refractory chronic lymphocytic leukaemia
Treatment phase:	Initial treatment
Restriction Level / Method:	<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
Clinical criteria:	The condition must have relapsed or be refractory to at least a line of treatment with a kinase inhibitor. AND The treatment must be as monotherapy AND Patient must not have previously received PBS-subsidised treatment with this drug for this condition.
Prescriber Instructions	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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Administrative Advice	<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 www.humanservices.gov.au</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		
Tablets, 100 mg, 120	1	5		

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Severity:	Relapsed or refractory
Condition:	Chronic lymphocytic leukaemia
PBS Indication:	Relapsed or refractory chronic lymphocytic leukaemia
Treatment phase:	Continuing treatment
Restriction Level / Method:	<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
Clinical criteria:	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
Administrative Advice	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.

9 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.

10 Sponsor's Comment

AbbVie appreciates 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 with the PBAC and Department of Health on ensuring provision of access to patients in this area of high unmet need.