

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

1 Purpose of Application

1.1 The submission requested a Section 85 Authority Required PBS listing for venetoclax for the treatment of relapsed/refractory chronic lymphocytic leukaemia (CLL) in patients with 17p deletion/TP53 mutation and patients with highly refractory disease.

2 Requested listing

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

Authority Required (abbreviated)

Relapsed/refractory chronic lymphocytic leukaemia in

- patients with 17p deletion AND/OR TP53 mutation OR
- patients with highly refractory disease (refractory to fludarabine-based regimens OR intolerant/inadequate response to B-cell receptor signal inhibitors OR received at least two prior lines of therapy (unless contraindicated), including at least one line of chemoimmunotherapy).

2.1 The evidence provided to support the listing of venetoclax was limited to its use as monotherapy. It may be appropriate to specify this in the restriction because, although not explicitly requested in the submission, the proposed listing would allow the use of venetoclax in combination with other therapies (e.g. rituximab) and there is an ongoing trial involving venetoclax in combination with rituximab.

2.2 The submission acknowledged that there were limited data to support the use of venetoclax in the subgroup of patients with TP53 mutation only (i.e. in the absence of 17p deletion). The ESC noted that, in the August 2016 addendum to the July 2016 PSD for idelalisib, PBAC had recommended priority be given to listing with reference to the 17p deletion over the TP53 mutation, with the latter recommended to be added for patients testing negative for the 17p deletion when it subsequently becomes available through the Medicare Benefits Schedule.

- 2.3 The proposed PBS restriction for “highly refractory” disease was intended to identify a patient population with no other suitable treatment options. However, the current wording would potentially allow venetoclax treatment as a second-line rather than last-line option in many patients with relapsed/refractory CLL. The ESC noted that the incurable nature of CLL meant that patients were likely to cycle through all available treatments.
- 2.4 Listing was requested on a cost-effectiveness basis compared to ofatumumab monotherapy (in patients with 17p deletion/TP53 mutation) and rituximab monotherapy (in patients with highly refractory disease). Given the differences between the PBS listed ofatumumab population and the proposed venetoclax population the comparison against ofatumumab was not considered relevant (see comparator section, below).

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

3 Background

- 3.1 The submission was made under the TGA/PBAC Parallel Process. The clinical evaluation report and delegate’s overview were available during the evaluation.
- 3.2 Venetoclax was registered on the ARTG on 5 January 2017 for:
- patients with relapsed or refractory chronic lymphocytic leukaemia (CLL) with 17p deletion, or
 - patients with relapsed or refractory CLL for whom there are no other suitable treatment options.
- 3.3 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”.
- 3.4 The PBAC has not previously considered venetoclax.
- 3.5 The sponsor has lodged a submission for consideration by MSAC under the streamlined co-dependent assessment pathway requesting MBS coverage of 17p deletion and TP53 mutation testing.

4 Clinical place for the proposed therapy

- 4.1 Chronic lymphocytic leukaemia (CLL) is the most common form of leukaemia and is characterised by the proliferation and accumulation of B-lymphocytes in the blood, bone marrow, lymph nodes, and spleen. Typical symptoms associated with CLL include swollen lymph nodes, pain, anaemia, infections, increased or unexplained bleeding/bruising, excessive nocturnal sweating and unintentional weight loss. Chronic lymphocytic leukaemia is generally a slowly progressing cancer with many patients managed with watchful waiting until symptoms develop. Treatment is typically non-curative with patients potentially receiving multiple lines of therapy as their disease becomes relapsed/refractory to their current treatment. Advanced CLL is associated with an increased risk of premature death.

- 4.2 The presence of a 17p deletion or TP53 mutation is associated with increased resistance to fludarabine-based therapies (typically used in first-line treatment regimens). Genetic markers are assessed at multiple time points over the disease course as mutation status may change over time (and exposure to active therapies) due to clonal evolution.
- 4.3 The submission positioned venetoclax as a second-line treatment option in patients with relapsed/refractory CLL who have a 17p deletion or TP53 mutation. The submission also positioned venetoclax as a third-line treatment option in patients with relapsed/refractory CLL without a 17p deletion or TP53 mutation. The submission noted that the intended place for venetoclax in this population is for patients with no other suitable treatment options.
- 4.4 The PBAC 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/refractory CLL proposed in the submission, and the relative place in comparison to ibrutinib and idelalisib if they were listed on the PBS.

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

5 Comparator

- 5.1 The submission nominated ofatumumab monotherapy as the main comparator in patients with 17p deletion/TP53 mutation. This was not an appropriate comparator as ofatumumab is only PBS-listed for first-line therapy in combination with chlorambucil (i.e. there is no overlap between the current PBS restriction of ofatumumab and the proposed PBS listing for venetoclax).
- 5.2 The ESC considered that the most relevant comparators to inform the cost effectiveness of venetoclax in the requested PBS population were idelalisib and ibrutinib, both of which have been under recent consideration by the PBAC for similar patient populations. In the event that neither of these products is subsequently listed, the ESC agreed that a comparison against standard care would also be informative. The July 2016 PBAC meeting recommended the listing of idelalisib, in combination with rituximab, for an overlapping population. [REDACTED]
- 5.3 The submission nominated rituximab monotherapy (as a proxy for best supportive care) as the main comparator in patients with highly refractory disease. Best supportive care is an appropriate comparator in patients with no other suitable treatment options. 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 (March and November 2015 idelalisib Public Summary Documents).

- 5.4 The current wording of the proposed restriction for “highly refractory” patients would potentially allow venetoclax treatment as a second-line treatment option. The appropriate comparator in this subpopulation is unclear.
- 5.5 The submission nominated ibrutinib and idelalisib with rituximab as secondary comparators. These were appropriate comparators. The PBAC considered that the main comparator of ofatumumab nominated in the submission was not relevant because there is no overlap in the treated populations for PBS funded use. 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.

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 presented clinical case studies and discussed how the drug would be used in practice, and addressed other matters in response to the Committee’s questions.
- 6.2 In particular, the clinician clarified differences including the side effect profiles of venetoclax, ibrutinib, and idelalisib, and discussed how these might guide prescribing choices in clinical practice.
- 6.3 The clinician also noted that the more lines of therapy a patient has been through, the more likely they are to have developed resistance to some treatments. Whether this will impact on the effectiveness of venetoclax, or whether venetoclax would be a more effective treatment if used earlier, remains unclear.
- 6.4 The PBAC considered that the hearing was informative as it provided a clinical perspective on treating patients in this developing setting.

Consumer comments

- 6.5 The PBAC noted and welcomed the input from individuals (40), health care professionals (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 easy administration (being a tablet), providing an additional treatment option for patients who have not had a good response with chemotherapy, and use of an Australian-developed product. The PBAC also noted comments that proposed venetoclax prolongs survival and improves quality of life with few known side effects; but that the submission did not provide supporting evidence.

Clinical trials

- 6.6 No head-to-head trials comparing venetoclax to nominated comparators were available. The submission was based on a series of naïve indirect comparisons:
 - 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.
- 6.7 The submission did not present literature searches for the two nominated main comparators (ofatumumab monotherapy, rituximab monotherapy). Studies for these treatments appeared to have been found incidentally in literature searches for ibrutinib and idelalisib. It is unclear whether the included studies for ofatumumab and rituximab monotherapy adequately represent their available evidence base.
- 6.8 Details of the studies presented in the submission are provided in Table 1.

Table 1: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Venetoclax studies		
M12-175	AbbVie Clinical Study Report (2015). A phase 1 study evaluating the safety and pharmacokinetics of ABT-199 in subjects with relapsed or refractory chronic lymphocytic leukemia and non-Hodgkin lymphoma.	Internal study report [Interim results]
	AbbVie Clinical Study Update (2016). Updated results of study M12-175 up to 10 June 2016.	Internal data [Interim results]
	Roberts AW et al (2016). Targeting BCL2 with venetoclax in relapsed chronic lymphocytic leukemia.	New England Journal of Medicine; 374: 311-322
M13-982	AbbVie Clinical Study Report (2015). A phase 2 open-label study of the efficacy of ABT-199 (GDC-0199) in subjects with relapsed/refractory or previously untreated chronic lymphocytic leukemia harbouring the 17p deletion.	Internal study report [Interim results]
	AbbVie Clinical Study Update (2016). Updated results of study M13-982 up to 10 June 2016.	Internal data [Interim results]
	Stilgenbauer S et al (2016). Venetoclax in relapsed or refractory chronic lymphocytic leukaemia with 17p deletion: a multicentre, open-label, phase 2 study.	The Lancet Oncology; 17(6): 768-778.
M14-032	AbbVie Clinical Study Report (2015). A phase 2 open-label study of the efficacy and safety of venetoclax (ABT-199/GDC-0199) in chronic lymphocytic leukemia subjects with relapsed or refractory to B-cell receptor signalling pathway inhibitor therapy.	Internal study report [Preliminary results]
	AbbVie Clinical Study Update (2016). Updated results of study M14-032 up to 10 June 2016.	Internal data [Interim results]
Ibrutinib studies		
RESONATE	Byrd JC et al (2014). Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia.	New England Journal of Medicine; 371: 213-223.
	Brown JR et al (2014). Updated efficacy including genetic and clinical subgroup analysis and overall safety in the phase 3 RESONATE™ trial of ibrutinib versus ofatumumab in previously treated chronic lymphocytic leukemia/small lymphocytic lymphoma.	Blood 124: 3331 [abstract only]
	NICE technology appraisal (2016). Ibrutinib for treating chronic lymphocytic leukaemia.	NICE website [ID749]
RESONATE-17	O'Brien S et al (2016). Ibrutinib for patients with relapsed or refractory chronic lymphocytic leukaemia with 17p deletion (RESONATE-17): a phase 2, open-label, multicentre study.	The Lancet Oncology; 17: 1409-1418.
Idelalisib + rituximab studies		
312-0116	Furman RR et al (2014). Idelalisib and rituximab in relapsed chronic lymphocytic leukemia.	New England Journal of Medicine; 370: 997-1007
	NICE technology appraisal (2015). Idelalisib for treating chronic lymphocytic leukaemia.	NICE website [ID764]

Source: Table B-3, p68-70 of the submission

6.9 The key features of the included studies are summarised in Table 2.

Table 2: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome	Use in modelled evaluation
Venetoclax studies						
M12-175	116	Phase 1, MC, OL Non-comparative Approximately 2 years median follow-up	High	Relapsed/refractory CLL	Treatment response, PFS, OS	Not used
M13-982	158	Phase 2, MC, OL Non-comparative Approximately 1-2 years median follow-up	High	Relapsed/refractory CLL with 17p deletion	Treatment response, PFS, OS	Responder rates (DD model)
M14-032	64	Phase 2, MC, OL Non-comparative Approximately 9-12 months median follow-up	High	Relapsed/refractory CLL with prior ibrutinib or idelalisib failure	Treatment response, PFS, OS	Survival rates (DDD model)
Pooled subgroups (Section C)	218	Pooled analysis of individual patient data for patients with 17p deletion/TP53 mutation in the M12-175, M13-982 and M14-032 studies; assessed PFS and OS				Survival rates (D model)
Ibrutinib studies						
RESONATE	391	Phase 3, MC, R, OL Ibrutinib vs ofatumumab Approximately 1-2 years median follow-up	Unclear	Relapsed/refractory CLL unsuitable for chemoimmunotherapy	Treatment response, PFS, OS	Ofatumumab PFS (D model)
RESONATE-17	144	Phase 2, MC, OL Non-comparative Approximately 1-2 years median follow-up	High	Relapsed/refractory CLL with 17p deletion	Treatment response, PFS, OS	Not used
Idelalisib + rituximab studies						
312-0116	220	Phase 3, MC, R, DB Idelalisib vs placebo (rituximab background) Approximately 1 year median follow-up	Low	Relapsed/refractory CLL unsuitable for chemoimmunotherapy	Treatment response, PFS, OS	Idelalisib responder rates (DD model) Rituximab survival rates (DDD model)

Abbreviations: CLL, chronic lymphocytic leukaemia; DB, double-blind; MC, multi-centre; OL, open-label; OS, overall survival; PFS, progression-free survival; R, randomised

Source: Constructed during the evaluation

6.10 The evidence base supporting the use of venetoclax is immature and was based on interim results from ongoing non-comparative Phase 1 and Phase 2 studies. As noted by the Canadian Agency for Drugs and Technologies in Health (CADTH), many chemotherapy regimens demonstrating positive results in single-arm Phase 2 studies do not translate into positive results in Phase 3 RCTs, and it is unclear whether the outcomes observed with venetoclax would be consistent in a randomised controlled trial (CADTH pan-Canadian Oncology Drug Review 10087, December 2016). No RCTs of venetoclax monotherapy (either ongoing or completed) were identified during the evaluation. However, one ongoing RCT was identified

comparing venetoclax in combination with rituximab versus bendamustine with rituximab (NCT02005471).

- 6.11 The included studies may not have been sufficiently similar in terms of study design (Phase 1/2 single arm studies versus Phase 3 RCTs) and patient populations (potential differences in prognostic mutations, prior treatment exposure, patient fitness and disease stage) to justify an indirect comparison.

Comparative effectiveness

- 6.12 Comparative effectiveness estimates relied on a naïve indirect comparison, which is not a reliable method for assessing comparative efficacy.
- 6.13 The key results of the indirect comparison between venetoclax and ofatumumab monotherapy in patients with 17p deletion/TP53 mutation are summarised in Table 3.

Table 3: Summary of the most recent efficacy results for venetoclax vs. ofatumumab in patients with 17p deletion/TP53 mutation

	M12-175	M13-982	RESONATE
	VEN 400 mg 17p del (N = 14)	VEN main cohort (N = 158)	OFAT 17p del (N = 64)
Median duration of treatment, months (range)			5 (NR) ¹
Median duration of follow-up, months (range)			16 (NR) ¹
Response rates			
Overall response rate, % (95% CI)		77.2 (69.9, 83.5)	NR
- Complete response, n (%)		29 (18.4)	NR
- Partial response, n (%)		93 (58.9)	NR
Progression-free survival			
Events n (%)			NR
Median PFS, months (95% CI)		27.2 (21.9, NE)	5.8 (NR) ²
KM estimate of PFS at 6 months, % (95% CI)			NR
KM estimate of PFS at 12 months, % (95% CI)		77 (69, 83)	17 (NR)
Overall survival			
Deaths n (%)			NR
Median OS, months (95% CI)		Not reached	NR
KM estimate of OS at 6 months, % (95% CI)			NR
KM estimate of OS at 12 months, % (95% CI)		87 (80, 91)	NR

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

¹ Median duration for all subjects (not reported for the subgroup)

² Results from 9-month analysis; not reported in 16-month analysis

Source: Compiled during the evaluation using the most recent investigator-assessed outcomes.

- 6.14 Based on the naïve indirect comparison, the submission claimed that venetoclax treatment was associated with numerically higher progression-free survival compared to ofatumumab monotherapy.
- 6.15 The submission also claimed to have conducted a matching adjusted indirect comparison of venetoclax (based on a pooled analysis of patients with 17p deletions in the venetoclax studies) versus ofatumumab. This analysis indicated that treatment with venetoclax was associated with substantially longer progression-free survival

compared to ofatumumab (adjusted HR █████; 95% CI █████, █████). The matching adjusted indirect comparison was poorly documented in the submission and estimates could not be independently verified during the evaluation.

- 6.16 The key results of the indirect comparison between venetoclax and idelalisib with rituximab in patients with 17p deletion/TP53 mutation are summarised in Table 4.

Table 4: Summary of the most recent efficacy results for venetoclax vs. idelalisib with rituximab in patients with 17p deletion/TP53 mutation

	M12-175	M13-982	312-0116
	VEN 400mg 17p del (N = 14)	VEN main cohort (N = 158)	IDEL + RITU 17p/TP53 subgroup (N = 46)
Median duration of treatment, months (range)	█████	█████	8.1 (0.3-19.5) ¹
Median duration of follow-up, months (range)	█████	█████	12.5 (0.3-25.1) ¹
Response rates			
Overall response rate, % (95% CI)	█████	77.2 (69.9, 83.5)	84.8 (NR)
- Complete response, n (%)	█████	29 (18.4)	0
- Partial response, n (%)	█████	93 (58.9)	(84.8)
Progression-free survival			
Events n (%)	█████	█████	NR
Median PFS, months (95% CI)	█████	27.2 (21.9, NE)	Not reached (12.3, NE)
KM estimate of PFS at 6 months, % (95% CI)	█████	█████	NR
KM estimate of PFS at 12 months, % (95% CI)	█████	77 (69, 83)	NR
Overall survival			
Deaths n (%)	█████	█████	NR
Median OS, months (95% CI)	█████	Not reached █████	Not reached (18.8, NE)
KM estimate of OS at 6 months, % (95% CI)	█████	█████	NR
KM estimate of OS at 12 months, % (95% CI)	█████	87 (80, 91)	NR

Abbreviations: 17p del, 17p deletion subgroup; 17p/TP53, 17p deletion/TP53 mutation subgroup; CI, confidence interval; IDEL, idelalisib; KM, Kaplan-Meier; NE, not evaluable; NR, not reported; OS, overall survival; PFS, progression-free survival; RITU, rituximab; VEN, venetoclax

¹ Median duration for all subjects (not reported for the subgroup)

Source: Compiled during the evaluation using the most recent investigator- or IRC-assessed outcomes.

- 6.17 Based on the naïve indirect comparison, the submission claimed that venetoclax treatment was associated with numerically higher complete response rates and numerically similar overall response rates compared idelalisib with rituximab.
- 6.18 The key results of the indirect comparison between venetoclax and ibrutinib in patients with 17 deletion/TP53 mutation are summarised in Table 5.

Table 5: Summary of the most recent efficacy results for venetoclax vs. ibrutinib in patients with 17p deletion/TP53 mutation

	M12-175	M13-982	RESONATE	RESONATE 17
	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 (%)	█	█	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: Compiled during the evaluation using the most recent investigator-assessed outcomes.

- 6.19 Based on the naïve indirect comparison, the submission claimed that venetoclax treatment was associated with numerically higher complete response rates and numerically similar survival outcomes compared to ibrutinib. It was also noted that venetoclax treatment was associated with numerically lower overall response rates.
- 6.20 The key results of the naïve indirect comparison between venetoclax and rituximab monotherapy in patients with highly refractory disease are summarised in Table 6.

Table 6: 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: Compiled during the evaluation using the most recent investigator- or IRC-assessed outcomes.

- 6.21 Based on the naïve indirect comparison, the submission claimed that venetoclax treatment was associated with numerically higher response rates and survival outcomes compared to rituximab monotherapy.

Comparative harms

- 6.22 The most frequently reported events associated with venetoclax treatment were blood and lymphatic disorders (anaemia, neutropenia, thrombocytopenia), gastrointestinal disorders (nausea, vomiting, constipation, diarrhoea), general disorders (fatigue, pyrexia), infections and infestations (upper respiratory tract infections), metabolism and nutrition disorders (hyperphosphataemia, hypomagnesaemia, hyponatraemia), nervous system disorders (headache), respiratory disorders (cough) and skin and subcutaneous disorders (rash). Many of the adverse events were of mild to moderate severity although approximately half the patients enrolled in the venetoclax trials experienced a serious adverse event (including atrial fibrillation, autoimmune haemolytic anaemia, febrile neutropenia, pyrexia, pneumonia, upper respiratory tract infection, fluid overload, prostate cancer, multi-organ dysfunction syndrome, and hyperkalaemia).
- 6.23 Adverse events leading to premature treatment discontinuation included autoimmune haemolytic anaemia, neutropenia, febrile neutropenia, thrombocytopenia, diarrhoea, vomiting, mucosal inflammation, multiple organ dysfunction syndrome, malignant neoplasm progression, Richter's syndrome, myelodysplastic syndrome, paraneoplastic pemphigus, respiratory failure and increased creatinine.

- 6.24 Treatment-related deaths due to tumour lysis syndrome (TLS) were reported in Study M12-175 which resulted in the development of a TLS monitoring program. No further TLS deaths have been reported in the venetoclax study program. The FDA recommended a warning for TLS for venetoclax in the US.
- 6.25 The submission presented a series of naïve indirect comparisons of safety outcomes between venetoclax and the nominated comparators. This is not a reliable method for assessing comparative safety. The incidence of adverse events was difficult to interpret given the substantial differences in treatment exposure between studies.
- 6.26 Based on the naïve indirect comparisons, the submission acknowledged that venetoclax was associated with a numerically higher incidence of Grade 3 or higher severity adverse events (require medical attention) compared to ofatumumab monotherapy and rituximab monotherapy.
- 6.27 Based on the naïve indirect comparisons, the submission claimed that venetoclax had a different but noninferior safety profile compared to ibrutinib as well as idelalisib with rituximab. It is unclear whether this claim was reasonable given the limited available data. Treatment with venetoclax appeared to be associated with higher rates of cytopenias that required medical attention compared to comparators:
- 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.
- 6.28 Comparisons of safety between venetoclax, ibrutinib and idelalisib with rituximab may be biased in favour of venetoclax because the ibrutinib and idelalisib trials included patients with a higher risk of cytopenias.
- 6.29 The submission acknowledged that venetoclax may have a higher risk of TLS compared to the other nominated treatments.
- 6.30 The submission did not provide an adequate assessment of safety from the broader venetoclax trial program outside the requested restriction. Limited adverse event data (in terms of number of patients treated and duration of therapy) are available for venetoclax treatment.

Benefits/harms

- 6.31 There was insufficient information to reliably quantify the benefits and harms of venetoclax compared to the nominated comparators (ofatumumab monotherapy, rituximab monotherapy; ibrutinib; idelalisib with rituximab).

Clinical claim

- 6.32 The submission described venetoclax as superior in terms of comparative efficacy, with inferior safety compared to ofatumumab in relapsed/refractory patients with a 17p deletion/TP53 mutation. Despite the limited evidence, this claim may be reasonable in terms of efficacy and safety. However, the magnitude of any benefit

was unclear. Furthermore, this has no direct relevance to the requested listing, given that ofatumumab was not a relevant comparator.

- 6.33 The submission described venetoclax as superior in terms of comparative efficacy, with a noninferior safety profile compared to idelalisib with rituximab in relapsed/refractory patients with a 17p deletion/TP53 mutation. The ESC advised that this claim was not adequately supported in terms of efficacy or safety, due to the limited evidence.
- 6.34 The submission described venetoclax as equivalent in efficacy and safety to ibrutinib in relapsed/refractory patients with a 17p deletion/TP53 mutation. The ESC advised that this claim was not adequately supported in terms of efficacy or safety, due to the limited evidence.
- 6.35 Given the issues with the data, the ESC considered it was not possible to reliably assess these claims in relation to the relevant comparators (idelalisib and ibrutinib), which is important given the context of a relatively common cancer, likely small but potentially important difference across these therapies, and stronger evidence being collected.
- 6.36 The submission described venetoclax as superior in terms of comparative efficacy, with inferior safety compared to rituximab monotherapy in patients with highly refractory disease. Despite the limited evidence, this claim may be reasonable in terms of efficacy and safety. However, the magnitude of any benefit was unclear.
- 6.37 The PBAC considered that the claims of comparative effectiveness between venetoclax and idelalisib or ibrutinib were not adequately supported by the data.
- 6.38 The PBAC considered that the claims of comparative safety between venetoclax and idelalisib or ibrutinib were not adequately supported by the data.

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

Economic analysis

- 6.39 The submission included a series of economic evaluations:
- a modelled cost-utility analysis assessing the value of venetoclax compared to ofatumumab monotherapy in patients with 17p deletion/TP53 mutation; and
 - 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.

6.40 The general structure of the cost-utility models is summarised in Table 7.

Table 7: Summary of model structure and rationale

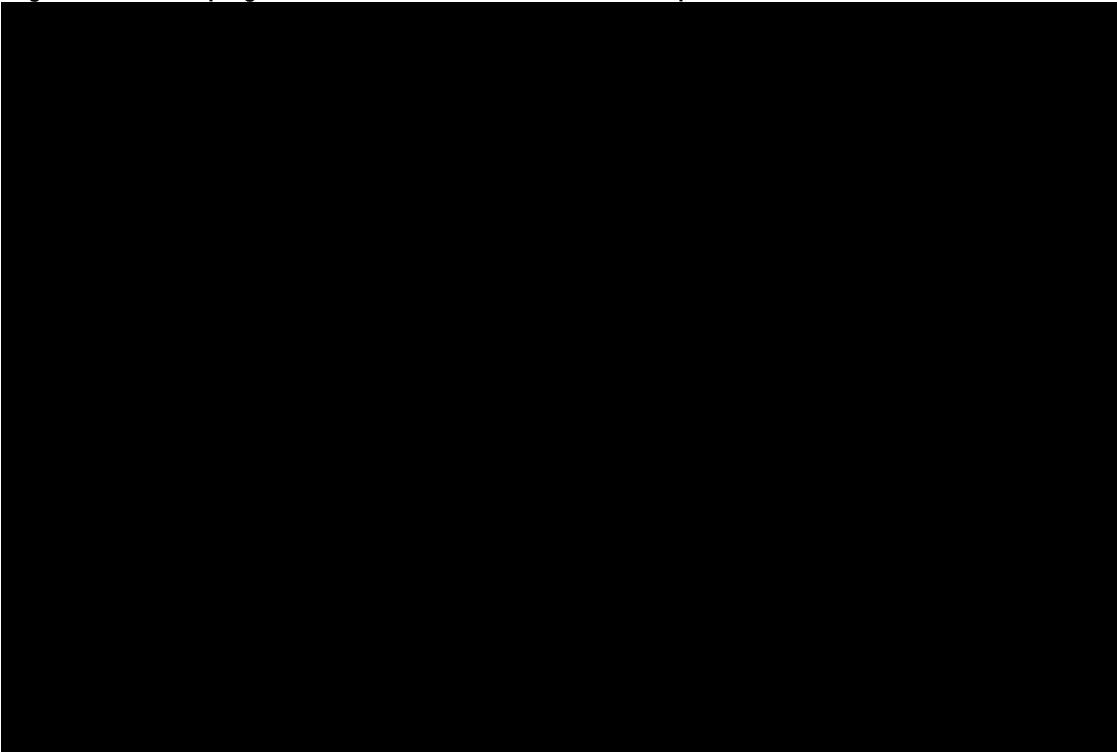
Methods used to generate results	Markov cohort expected value analysis
Time horizon	10 years
Cycle length	4 weeks; with half-cycle correction
Health states	Pre-progression, post-progression, dead
Outcomes	Complete responders, life years, quality-adjusted life years
Transition probabilities: Venetoclax vs ofatumumab	Based on a partitioned survival analysis of venetoclax vs. ofatumumab. Progression-free and overall survival probabilities for venetoclax were derived from extrapolated survival curves from the pooled venetoclax study populations with 17p deletion/TP53 mutation. Progression-free survival probabilities for ofatumumab were derived from the venetoclax survival data based on a matching adjusted indirect comparison between venetoclax and ofatumumab. Overall survival probabilities for ofatumumab were derived from the venetoclax survival data based on an unadjusted indirect comparison between venetoclax and FCR therapy.
Transition probabilities: Venetoclax vs rituximab	Based on a partitioned survival analysis of venetoclax vs. rituximab monotherapy. Progression-free and overall survival probabilities for venetoclax were derived from extrapolated survival curves from Study M14-032. Progression-free and overall survival probabilities for rituximab monotherapy were derived from extrapolated survival curves from Trial 312-0116.
Discount rate	5% for costs and outcomes
Software package	Excel 2013

Abbreviations: FCR, fludarabine, cyclophosphamide, rituximab

Source: constructed during the evaluation

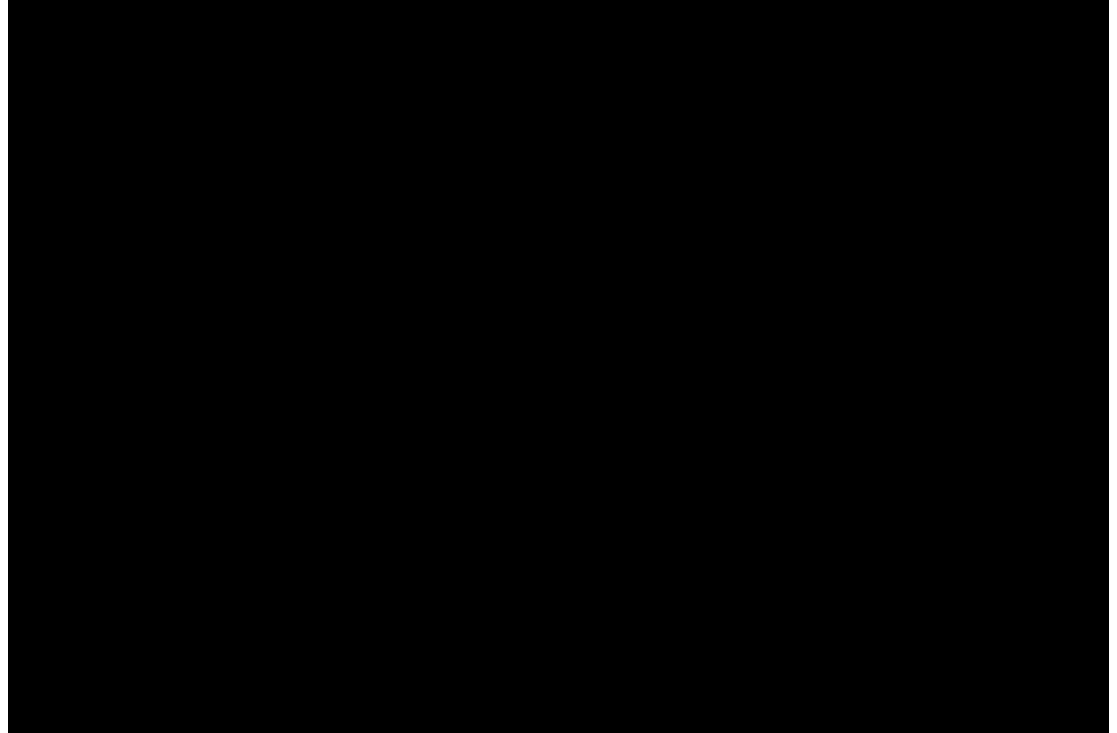
- 6.41 The submission also presented a simple modelled cost-effectiveness analysis (cost per complete responder) assessing the value of venetoclax compared to idelalisib with rituximab in patients with 17p deletion/TP53 mutation. The model horizon was 2 years (no discounting) and included drug costs, administration costs and monitoring costs.
- 6.42 The submission did not present an economic analysis comparing venetoclax with ibrutinib monotherapy. The pre-PBAC response provided a cost-minimisation analysis, assuming the doses of venetoclax monotherapy and ibrutinib monotherapy in the respective studies were equi-effective and accounting for the cost of TLS prophylaxis with venetoclax.
- 6.43 The submission claimed that treatment with venetoclax was associated with a median overall survival gain of 3.7 years compared to ofatumumab monotherapy (see Figure 1) and 4.0 years compared to rituximab monotherapy (see Figure 2). The estimated survival gain had an overwhelming impact on the economic evaluation with the models being insensitive to all other variables that were not directly related to survival gain. The ESC considered that the survival comparisons presented in the submission were unlikely to give a reliable estimate of any survival benefit associated with venetoclax treatment, given the uncertainty around the results used as the basis for the extrapolation.

Figure 1: Modelled progression-free and overall survival for comparison of venetoclax versus ofatumumab



Abbreviations: OFAT, ofatumumab; OS, overall survival; PFS, progression-free survival; VEN, venetoclax
Source: Constructed during the evaluation using Economic Evaluation versus Ofatumumab spreadsheet

Figure 2: Modelled progression-free and overall survival for comparison of venetoclax versus rituximab



Abbreviations: OS, overall survival; PFS, progression-free survival; RITUX, rituximab; VEN, venetoclax
Source: Constructed during the evaluation using Economic Evaluation versus BSC spreadsheet

6.44 Key issues with the cost utility models are summarised in Table 8.

Table 8: Key drivers of the model

Description	Method or value	Impact
Treatment efficacy	<p>Comparative treatment efficacy estimates for patients with 17p deletion/TP53 mutation were derived from a matching adjusted indirect comparison of venetoclax versus ofatumumab monotherapy. The indirect analysis was based on limited data and was poorly documented with inconsistent claims. The results of these analyses should not be considered reliable.</p> <p>Comparative treatment efficacy estimates for patients with highly refractory disease were derived from a naïve indirect comparison of venetoclax versus rituximab monotherapy. A naïve indirect comparison is not a reliable method for assessing comparative efficacy as it does not account for differences between studies which may affect survival outcomes.</p>	<p>High (for ofatumumab comparison), favours venetoclax</p> <p>High (for rituximab comparison), favours venetoclax</p>
Extrapolation method	<p>The submission used Weibull functions to extrapolate progression-free and overall survival for venetoclax in patients with 17p deletion/TP53 mutation. Extrapolated ofatumumab curves were synthesised based on inverse hazard ratios (see treatment efficacy) applied to the venetoclax survival curves. Survival models were based on limited observed data (approximately 1-2 years). It was not reasonable to synthesise an ofatumumab curve based on the matching adjusted indirect comparison.</p> <p>The submission used exponential functions to extrapolate progression-free and overall survival for venetoclax in patients with highly refractory disease. Survival curves for rituximab monotherapy were independently extrapolated based on a Weibull function. Survival models were based on limited observed data (approximately 9-12 months). Survival curves were likely to be affected by differences in baseline risk between the different sources studies.</p> <p>A substantial proportion of estimated overall survival gain with venetoclax is due to increased survival in the post-progression state which may not be plausible given that treatment is expected to be discontinued at progression.</p>	<p>Low (for ofatumumab comparison), variable direction</p> <p>High (for rituximab comparison), variable direction</p>
Post-progression survival	<p>Post-progression survival was estimated based on the difference between two independently derived extrapolated survival curves (overall survival and progression-free survival). A substantial proportion of estimated overall survival gain with venetoclax is due to increased survival in the post-progression state which may not be reasonable given that treatment is expected to be discontinued at progression.</p>	<p>High (for both comparisons), favours venetoclax</p>
Time horizon	<p>The submission nominated a 10-year time horizon which was consistent with time horizons previously proposed in the ibrutinib and idelalisib PBAC submissions. The PBAC has suggested that shorter time horizons may be appropriate in populations with relapsed/refractory CLL.</p>	<p>Moderate (for ofatumumab comparison), favours venetoclax</p> <p>High (for rituximab comparison), favours venetoclax</p>
Pre-progression health state	<p>Based on a post-hoc analysis of EQ-5D data from the M13-982 and M14-032 trials. The post-hoc analysis was poorly documented and utility estimates from the venetoclax trials were higher than those</p>	<p>Moderate (for both comparisons), favours venetoclax</p>

Description	Method or value	Impact
utility	presented in other published utility studies for relapsed/refractory CLL.	

Source: compiled during the evaluation

- 6.45 The key issue with the modelled cost-effectiveness analysis (cost per responder) was the choice of health outcome for the venetoclax versus idelalisib with rituximab comparison. The analysis was based on investigator-assessed complete responders, which numerically favoured venetoclax.
- 6.46 This approach may be unreasonable as it assumes no value for partial responders. Expanding the analysis to overall responders (complete plus partial) switched the direction of the results with venetoclax having numerically lower response rates compared to idelalisib with rituximab. Additionally, investigator-assessed outcomes were generally more favourable than centrally-assessed outcomes for venetoclax (18.4% vs. 7.5%). Limiting the analysis to centrally-assessed outcomes substantially reduced the numerical difference in complete response rates between treatments.
- 6.47 The results of the economic analysis comparing venetoclax to ofatumumab monotherapy in 17p deletion/TP53 mutation patients is summarised in Table 9.

Table 9: Modelled economic analyses (venetoclax vs ofatumumab monotherapy)

	Venetoclax	Ofatumumab	Increment
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
LYs	[REDACTED]	1.008	[REDACTED]
QALYs	[REDACTED]	0.793	[REDACTED]
Incremental cost per LY gained			\$ [REDACTED]
Incremental cost per QALY gained			\$ [REDACTED]

Abbreviations: LY, life year; QALY, quality-adjusted life year

Source: Table D-15 (p 220) of the submission

- 6.48 Based on the economic model, treatment with venetoclax was associated with a cost per QALY gained of \$45,000 – \$75,000 compared to ofatumumab monotherapy in patients with 17p deletion/TP53 mutation. This estimate should not be considered reliable due to uncertainty regarding modelled survival data (particularly treatment efficacy estimates).
- 6.49 Sensitivity analyses indicated that the model was most sensitive to assumptions regarding post-progression treatment effects.
- 6.50 The results of the economic analysis comparing venetoclax to rituximab monotherapy in patients with highly refractory disease is summarised in Table 10.

Table 10: Modelled economic analyses (venetoclax vs rituximab monotherapy)

	Venetoclax	Rituximab	Increment
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
LYs	[REDACTED]	1.231	[REDACTED]
QALYs	[REDACTED]	0.919	[REDACTED]
Incremental cost per LY gained			\$ [REDACTED]
Incremental cost per QALY gained			\$ [REDACTED]

Abbreviations: LY, life year; QALY, quality-adjusted life year

Source: Table DDD-10 (p 237) of the submission

- 6.51 Based on the economic model, treatment with venetoclax was associated with a cost per QALY gained of \$75,000 – \$105,000 compared to rituximab monotherapy in patients with highly refractory disease. This estimate should not be considered reliable due to uncertainty regarding modelled survival data (particularly treatment efficacy estimates).
- 6.52 Sensitivity analyses indicated that the model was most sensitive to assumptions regarding post-progression treatment effects, extrapolation methods for progression-free survival and time horizon.
- 6.53 The results of the economic analysis comparing venetoclax to idelalisib with rituximab in patients with 17p deletion/TP53 mutation is summarised in Table 11.

Table 11: Modelled economic analyses (venetoclax vs idelalisib with rituximab)

	Venetoclax	Idelalisib with rituximab	Increment
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Proportion of patients with complete response	18.4	0.0	18.4
Incremental cost per complete response			\$ [REDACTED]

Source: Table DD-10 (p 227-228) of the submission

- 6.54 Based on the economic model, treatment with venetoclax was associated with a cost per complete responder of \$105,000 – \$200,000 compared to idelalisib with rituximab in patients with 17p deletion/TP53 mutation. The use of responder outcomes in the economic analysis was difficult to interpret without additional data on the duration of response and the association with progression-free survival and overall survival.
- 6.55 Sensitivity analyses indicated that the model was sensitive to the estimated price of idelalisib and the choice of health outcome. Idelalisib with rituximab dominated venetoclax when the health outcome was switched from complete responders to overall responders.

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

Drug cost/patient/course

- 6.56 The cost of venetoclax and comparators per patient per 24-week period are summarised in Table 12. Treatment is ongoing for venetoclax and idelalisib. Treatment is limited to 24 weeks for rituximab and ofatumumab. The submission did not estimate the costs of ibrutinib therapy.

Table 12: 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 submission) ^a Weeks 9-24 = \$ [REDACTED] (calculated using effective DPMQ for maintenance pack x 112 days per 16 weeks/30 days treatment per pack)	\$ [REDACTED]
Ofatumumab monotherapy	Weeks 1-4 = \$22,018 (weighted public/private published DPMA for 300 mg x 1 week + weighted public/private DPMA for 1000 mg x 2 x 3 weeks) ^b Weeks 5-8 = \$27,838 (weighted average public/private published DPMA for 1000 mg x 4 infusions) ^b Weeks 9-24 = \$27,838 (weighted public/private published DPMA for 1000 mg x 4 infusions over 16 weeks) ^b	\$77,693
Rituximab monotherapy	Weeks 1-4 = \$7,498.41 (weighted public/private DPMA for loading dose x 1 infusion + weighted public/private DPMA for maintenance dose x 1 infusion) ^c Weeks 5-8 = \$7,881.73 (weighted public/private DPMA for maintenance dose x 2 infusions) ^c Weeks 9-24 = \$15,764.46 (weighted public/private DPMA for maintenance dose x 4 infusions) ^c	\$31,144
Idelalisib plus rituximab	Idelalisib: \$30,241.06 (Canadian price for idelalisib x 168 days per 24 weeks/30 days treatment per assumed pack size) ^d Rituximab: \$31,144 (assumed to be the same as rituximab monotherapy)	\$61,385
Subsequent 24 weeks		
Venetoclax	Effective DPMQ for maintenance pack x 168 days per 24 weeks/30 days treatment per pack	\$ [REDACTED]
Ofatumumab monotherapy	No subsequent costs	
Rituximab monotherapy	No subsequent costs	
Idelalisib plus rituximab	Idelalisib: \$30,241.06 (Canadian price for idelalisib x 168 days per 24 weeks/30 days treatment per assumed pack size) ^d Rituximab: No subsequent costs	\$30,241

^a The submission assumed that in weeks 5-8, [REDACTED]% of the cost would be attributed to the maintenance pack and [REDACTED]% of patients would be treated with 1 week of the 10 mg and 50 mg dose hold packs (split 50:50) and 3 weeks of the maintenance pack

^b The DPMA for ofatumumab on the PBS is based on a maximum amount of 1000 mg. The submission assumed the DPMA for 2000 mg was 2 x DPMA for 1000 mg.

^c Weighted public/private DPMA for the loading dose (375 mg/m²) and maintenance dose (500 mg/m²) were calculated using the average body surface area of 1.93m² and using the PBS item numbers 4615X (public) and 7259C (private).

^d Idelalisib is not currently listed on the PBS. The submission estimated the DPMQ using the published Canadian price for 28 days converted into Australian dollars and the associated dispensing fees to obtain a DPMQ for a 30 day pack.

Source: 'Economic evaluation versus BSC', 'Economic evaluation versus Ofatumumab' and 'Economic evaluation versus idelalisib' Excel spreadsheets of the submission

Estimated PBS usage & financial implications

6.57 This submission was not considered by DUSC. The submission used an epidemiological approach to estimate the utilisation/financial implications associated with the PBS listing of venetoclax for the treatment of relapsed/refractory CLL in patients with 17p deletion/TP53 mutation and patients with highly refractory disease.

Table 13: Estimated utilisation and cost to the PBS in the first five years of listing

	Year 1 (2017)	Year 2 (2018)	Year 3 (2019)	Year 4 (2020)	Year 5 (2021)
Incident patients with relapsed/ refractory CLL	█	█	█	█	█
Patients with 17p deletion (32.8%) ^a	█	█	█	█	█
Patients TP53 mutation (4.0%) ^a	█	█	█	█	█
Patients with highly refractory disease (12.7%) ^b	█	█	█	█	█
Venetoclax uptake rate (59.14%)	█	█	█	█	█
Continuing patients (all patients assumed to have 2 years treatment)	-	█	█	█	█
Total patients receiving venetoclax	█	█	█	█	█
Titration scripts	█	█	█	█	█
Dose hold script	█	█	█	█	█
Maintenance scripts	█	█	█	█	█
Total venetoclax scripts per year	█	█	█	█	█
Cost of venetoclax (effective DPMQ)	\$ █	\$ █	\$ █	\$ █	\$ █
Patient co-payments	-\$ █	-\$ █	-\$ █	-\$ █	-\$ █
Substituted therapies (published DPMQ less co-pay)	-\$ █	-\$ █	-\$ █	-\$ █	-\$ █
TLS prophylaxis (drug costs) ^c	\$ █	\$ █	\$ █	\$ █	\$ █
Net cost to PBS/RPBS	\$ █	\$ █	\$ █	\$ █	\$ █
TLS prophylaxis (MBS monitoring costs)	\$ █	\$ █	\$ █	\$ █	\$ █
Infusion costs for substituted therapies	-\$ █	-\$ █	-\$ █	-\$ █	-\$ █
Net cost to government	\$ █	\$ █	\$ █	\$ █	\$ █

Abbreviations: CLL, chronic lymphocytic leukaemia; DPMQ, dispensed price maximum quantity; TLS, tumour lysis syndrome

^a Proportion of patients with 17p deletion (36.5%) or TP53 mutation (4.5%) adjusted for treatment rate (█%)

^b Proportion of patients without 17p deletion or TP53 mutation (63.5%) with no other suitable options (█%)

^c There was an error in the calculation as the submission did not incorporate the price of allopurinol. The impact on financial estimates was minor and not corrected during evaluation.

Source: Tables E-1 to E-6 pp240-246, Table E-13 p252, Table E-16 p254, Table E-18 p256 and 'Financial Implications – Section E' Excel workbook of the submission

- 6.58 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). The estimated cumulative cost to government after accounting for TLS prophylaxis and infusion costs with substituted therapies was \$30 - \$60 million based on the effective price (published price, \$60 - \$100 million).
- 6.59 The ESC considered that the estimated cost of listing venetoclax on the PBS was highly uncertain due to the inappropriate cost-offsets for ofatumumab monotherapy (not the appropriate comparator) and rituximab monotherapy (not an appropriate cost-offset when used as a proxy for best supportive care). The submission also likely underestimated the eligible patient populations as it did not account for prevalent CLL patients initiating first-line treatment in later years, did not account for patients developing a 17p deletion/TP53 mutation after multiple lines of therapy, and did account for patients becoming highly refractory after multiple lines of therapy. As a consequence, the estimated net cost to the PBS is likely to exceed \$20 - \$30

million per year.

- 6.60 The pre-PBAC response agreed with the ESC that the claims for ofatumumab and rituximab cost-offsets for patients with 17p deletion and highly refractory disease, respectively, were not adequately justified and were removed. The pre-PBAC response also changed the epidemiological basis for its utilisation and financial estimates from an incidence-based approach to a prevalence-based approach, which significantly increased the estimated uptake and potential financial cost to the PBS, but these revised estimates were not independently verified.

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

- 6.61 The submission claimed that the availability of venetoclax would not have a substantial impact on the utilisation of 17p deletion and TP53 mutation testing as it is already being used to identify chemoimmunotherapy resistance and to provide prognostic information. This claim was consistent with guideline recommendations (ESMO, NCCN) but responses from the sponsor-commissioned physician survey suggested that testing is more sporadic in clinical practice.
- 6.62 Estimates from the co-dependent MSAC submission indicated that subsidising testing for 17p deletion/TP53 mutation would fund less than 10,000 tests over five years with a cumulative cost of less than \$10 million. These estimates were uncertain because they did not adequately account for prevalent CLL patients initiating first-line treatment in later years, did not account for repeated testing over the course of the disease and made unsupported assumptions regarding the proportion of tests funded under the MBS.

Quality Use of Medicines

- 6.63 The submission acknowledged the risk of tumour lysis syndrome associated with venetoclax as well as the potential risk of medication error during the initial titration phase for venetoclax. To address this issue, the sponsor will undertake risk communication activities with patients and physicians.

Financial Management – Risk Sharing Arrangements

- 6.64 The sponsor expressed a willingness to enter into a risk share arrangement to address the financial uncertainty associated with the PBS listing of venetoclax.
- 6.65 The sponsor requested a special pricing arrangement, where the sponsor would provide a confidential ■% rebate to the published price of venetoclax.

7 PBAC Outcome

- 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.

- 7.2 The PBAC considered that the wording of the restriction would need to be revised once the clinical place of venetoclax is clarified. The PBAC considered that it is likely to be important that the restriction specifically addresses the use of venetoclax as monotherapy (compared to combination therapy), and that the intended line of therapy in patients with highly refractory disease (for example, second-line or third-line, or after failure of all other lines) should be explicit.
- 7.3 The PBAC considered that the clinical place of venetoclax in clinical practice remained unclear. In particular, the Committee was interested in the place of venetoclax compared to ibrutinib and idelalisib, both of which have recently been considered by the PBAC for listing in similar populations. The PBAC considered that the relative positioning of these three products was relevant to their consideration of venetoclax, including for the purpose of identifying the most appropriate comparator for venetoclax. The PBAC also noted the comment in the pre-PBAC response that no more data were forthcoming for venetoclax in the monotherapy setting, rather current ongoing trials were for venetoclax as part of combination therapy. The PBAC considered that the place in clinical practice of monotherapy was unclear given the possibility of combination therapy. Further, the PBAC noted that there may be a place for venetoclax to be used in an earlier line, when patients are likely to be more responsive to treatment.
- 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.
- 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.
- 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. In particular, the PBAC did not

consider that the incremental cost per extra responder for the comparison against idelalisib provided a clear basis for a recommendation to list, either in terms of interpreting the value of an extra responder or in terms of being confident that the numerical difference in response rates across the studies represented a true difference in effectiveness across the two medicines.

7.7 Overall, the PBAC considered that there were a number of areas of uncertainty, stemming mostly from the issues around the comparator and clinical place of venetoclax, which would need to be best addressed to enable a more completely informed consideration. In particular PBAC considered that the following should be addressed:

- a review of the clinical place of venetoclax relative to ibrutinib and idelalisib, including the line of therapy in which venetoclax would most likely be used, and the likely sequential use of venetoclax, idelalisib and ibrutinib. Given that the pre-PBAC response noted no new trials are planned for venetoclax monotherapy, any resubmission should also address whether venetoclax is more likely to be used as combination therapy, either with ibrutinib, or idelalisib, or any other product such as rituximab;
- the nomination of the most relevant comparator, as informed by the relative clinical places of venetoclax, idelalisib, and ibrutinib;
- a review of the evidence assessing the comparative effectiveness and safety of venetoclax in the common population relative to the most relevant comparator, being idelalisib and/or ibrutinib, together with a review of the relevant claims of superiority, non-inferiority or inferiority;
- in the event of that a cost-minimisation approach is taken between venetoclax and its comparator(s), the basis for estimating equi-effective doses, taking into appropriate consideration any differences in titration, treatment duration, and costs of preventing or managing venetoclax toxicity such as TLS; and
- updated estimates of utilisation and financial implications, calculated to reflect the review of the clinical place of venetoclax.

7.8 The PBAC noted that this submission is not eligible for an Independent Review, as the submission was not rejected.

Outcome:

Deferred

8 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.

9 Sponsor's Comment

AbbVie is committed to working with the PBAC to clarify the issues raised in order to ensure Australian patients receive timely access to venetoclax as a funded treatment

option for certain patients with Chronic Lymphocytic Leukaemia (CLL).

AbbVie however asserts that ofatumumab was a valid comparator as it is TGA approved for treatment of R/R CLL patients representing a basket of therapies used in the absence of PBS listed treatments. The decision was aligned with PBAC Guidelines and precedent evaluations.

AbbVie also wishes to clarify PSD paragraph 6.35. This statement refers to ongoing clinical trials for the combination of venetoclax and rituximab in R/R CLL, rather than for venetoclax monotherapy which is the subject of this submission.