**5.18 VENETOCLAX,  
Tablet 10 mg, 50 mg and 100 mg,   
Venclexta®, AbbVie Pty Ltd**

# Purpose of application

* 1. The submission requested a General Schedule (Authority Required – Telephone) listing of venetoclax plus rituximab for the treatment of patients with relapsed or refractory chronic lymphocytic leukaemia (CLL) who are unsuitable for treatment or retreatment with a purine analogue. The PBAC has not previously considered use of venetoclax in combination with rituximab. Submissions for venetoclax monotherapy were considered by the PBAC at the March 2017, July 2017 and November 2017 PBAC meetings.
  2. The listing was requested on a cost-minimisation basis compared to ibrutinib monotherapy.

**Table 1: Key components of the clinical issue addressed by the submission**

| Component | Description |
| --- | --- |
| Population | Patients with relapsed/refractory CLL considered unsuitable for treatment or retreatment with a purine analogue. |
| Intervention | * Venetoclax 400 mg PO daily until disease progression, unacceptable toxicity, or a maximum of 24 months (after completion of a 5-week dose titration). * Six cycles of rituximab administered by IV infusion every 28 days (375 mg/m2 for Cycle 1, 500 mg/m2 Cycles 2 to 6); commencing after 5-week venetoclax titration. |
| Comparator | Ibrutinib monotherapy 420 mg per day until disease progression or unacceptable toxicity. |
| Outcomes | Progression-free survival, overall survival, response rates, undetectable MRD, safety. |
| Clinical claim | Venetoclax plus rituximab is non-inferior in terms of efficacy to ibrutinib monotherapy.  Venetoclax plus rituximab has a different and non-inferior safety profile to ibrutinib monotherapy. |

Source: Table 8, p.24 of the submission.

Abbreviations: CLL, chronic lymphocytic leukaemia; PO, per oral; IV, intravenous; MRD, minimal residual disease.

# Requested listing

* 1. The proposed restrictions are presented in abbreviated form below. Secretariat suggestions and additions are in italics and strikethrough is used for deletions. It was noted the first 7 days of monotherapy at 400 mg daily (week 5 of the titration period) is missing from the continuing treatment restriction below. The Pre-PBAC Response included additional wording to the continuing treatment restriction to address this issue, highlighted in grey. The PBAC considered an Authority Required (telephone) listing for the initial and continuing criteria was appropriate.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Name, restriction, manner of administration, form** | **Max. Qty (packs)** | **No. of repeats** | **DPMQ\*** | **Proprietary name and manufacturer** |
| Venetoclax tablets, starting pack  (10 mg x14, 50 mg x7, 100 mg x7, 100 mg x14)  Venetoclax 10 mg tablet, 14  (dose hold pack)  Venetoclax 50 mg tablet, 7  (dose hold pack)  Venetoclax  100 mg tablet, 120 | 1  1  1  1 | 0  0  0  *5* | $''''''''''''''''''''  $''''''''''''''''  $'''''''''''''''''  $'''''''''''''''''''' | Venclexta®  AbbVie Pty Ltd |

\*published

**Initial treatment (first 4 weeks titration period)**

|  |  |
| --- | --- |
| **Category / Program** | GENERAL – General Schedule (Code GE) |
| **Prescriber type:** | Dental Medical Practitioners Nurse practitioners Optometrists  Midwives |
| **Episodicity:** | NA |
| **Severity:** | ~~Relapsed or refractory~~ |
| **Condition:** | Chronic lymphocytic leukaemia |
| **PBS Indication:** | ~~Relapsed or refractory~~ *~~c~~Chronic* lymphocytic leukaemia ~~in patients considered unsuitable for treatment or retreatment with a purine analogue~~ |
| **Treatment phase:** | Initial treatment |
| **Restriction Level / Method:** | Restricted benefit  Authority Required - In Writing  ~~Authority Required - Telephone~~  Authority Required – Emergency  Authority Required - Electronic  Streamlined |
| **Treatment criteria:** | ~~Must be under the direct supervision of a haematologist or medical oncologist.~~ |
| **Clinical criteria:** | The treatment ~~Starting pack~~ must be used as monotherapy,  **AND**  The condition must have relapsed or be refractory to at least one prior therapy,  **AND**  Patient must have a WHO performance status of 0 or 1,  **AND**  Patient must not have previously received PBS-subsidised treatment with this drug,  **AND**  Patient must be considered unsuitable for treatment or retreatment with a purine analogue. |
| **Population criteria:** | A patient must be considered unsuitable for treatment or retreatment with a purine analogue as demonstrated by at least one of the following:  a) Failure to respond (stable disease or disease progression on treatment), or a progression-free interval of less than 3 years from treatment with a purine analogue-based therapy and anti-CD20-containing chemoimmunotherapy regimen after at least two cycles;  b) Age is 70 years or older;  c) Age is 65 years or older and the presence of comorbidities (Cumulative Illness Rating Scale of 6 or greater, or creatinine clearance of less than 70 mL/min) that might place the patient at an unacceptable risk for treatment-related toxicity with purine analogue-based therapy, provided they have received one or more prior treatment including at least two cycles of an alkylating agent-based (or purine analogue-based) anti-CD20 antibody-containing chemoimmunotherapy regimen;  d) History of purine analogue-associated autoimmune anaemia or autoimmune thrombocytopenia;  e) Evidence of one or more 17p chromosomal deletions demonstrated by *fluorescence in situ hybridisation (*FISH*)*. |

**Dose holding (first 2 weeks titration period if hold dose needed)**

|  |  |
| --- | --- |
| **Treatment phase:** | ~~Initial (as required)~~ *Continuing treatment* |
| **Clinical criteria:** | *The treatment must be used 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 ~~using the Starting pack dispensed through PBS code XXX~~ *for this condition*. |

**Continuing treatment (week 5 titration period [monotherapy] + maintenance dose [in combination with rituximab for 6 cycles])**

|  |  |
| --- | --- |
| **Treatment phase:** | Continuing *treatment* |
| **Clinical criteria:** | Patient must have previously received PBS-subsidised treatment with this drug for this condition,  **AND**  The treatment must be as monotherapy for 7 days, then in combination with rituximab for *up to* a maximum of six cycles *unless rituximab is contraindicated, followed by monotherapy,*  **AND**  ~~Patients should continue~~ *~~venetoclax~~* ~~VTX for a maximum of 24 months and 7 days or until disease progression or unacceptable toxicity, whichever occurs first.~~  *Patient must not develop progressive disease whilst receiving PBS-subsidised treatment with this drug for this condition,*  ***AND***  *Patient must not receive more than 24 months and 7 days of treatment under this restriction.* |

* 1. The requested listing is narrower than the proposed TGA indication, which does not require patients to be unsuitable for treatment or retreatment with a purine analogue.
  2. The requested restriction is narrower than the inclusion criteria for the MURANO trial, which did not require patients to be unsuitable for treatment or retreatment with a purine analogue.
  3. The criteria to define patients unsuitable for treatment or retreatment with a purine analogue are identical to the restriction for ibrutinib.
  4. The proposed venetoclax restriction differs, but overlaps with the idelalisib with rituximab restriction, which specifies patients considered inappropriate for chemoimmunotherapy due to previous severe neutropenia, previous severe thrombocytopenia, or evidence of 17p deletion by FISH. The restriction for idelalisib plus rituximab also requires patients to be less fit (based on a comorbidity rating scale; CIRS>6).
  5. Venetoclax is administered according to a weekly dose titration schedule to the recommended daily dose of 400 mg over a period of 5 weeks. The dose titration schedule involves the administration of venetoclax as monotherapy over this period with the schedule proposed in the submission consistent with that presented in the draft Product Information (PI). Rituximab is then co-administered every 28 days for six cycles after the dose titration period is complete. Consistent with the Venclexta® starter pack, the initial restriction provides treatment for weeks 1 to 4 of the dose titration schedule only. However, an additional week of the 400 mg monotherapy is required as part of the dose titration schedule in the continuing restriction before co-administration with rituximab is commenced. The exclusion of week 5 of the dose titration schedule from the current form of the Venclexta® starter pack and the initial restriction would increase the potential for confusion with the required venetoclax dose titration regimen. The continuing treatment restriction was updated in the Pre-PBAC Response to allow for 7 days monotherapy venetoclax before co-administration with rituximab.
  6. The proposed continuing restriction limits treatment with venetoclax to 24 months.
  7. The ESC noted that there may be a subset of patients unsuitable for or intolerant of rituximab therapy which is required to be used in combination with venetoclax for six cycles after five weeks of monotherapy titration; and advised that consideration should be given to changing the proposed restriction to allow subsidised access for these patients. The Pre-PBAC Response noted the approved TGA indication for venetoclax monotherapy does not support a finite treatment duration.
  8. The submission did not propose a grandfathering restriction. However, the submission requested, should there be an early access program for venetoclax following TGA approval, that eligible patients are grandfathered across to PBS funded venetoclax. The ESC advised that the early access program should accord with the proposed PBS restriction rather than the TGA approval and that a grandfathering restriction could then be proposed by the sponsor.
  9. The Pre-PBAC Response proposed the following amended wording for the restriction to prevent sequential use of venetoclax plus rituximab and ibrutinib, if the submission was recommended for use in second-line only:

Patient must not have received prior treatment with ibrutinib; OR

Patient must have developed intolerance to ibrutinib of a severity necessitating permanent treatment withdrawal.

The PBAC did not agree with this proposal and considered that sequential use is likely to be clinically appropriate.

*For more detail on the PBAC’s view, see Section 7 PBAC Outcome.*

# Background

## Registration status

* 1. Venetoclax for use as monotherapy was registered on the ARTG on 5 January 2017 for:
* treatment of patients with relapsed or refractory chronic lymphocytic leukaemia (CLL) with 17p deletion, or
* treatment of patients with relapsed or refractory CLL for whom there are no other suitable treatment options.

Note to indications. The indications are approved 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.

* 1. Venetoclax plus rituximab was submitted under the parallel TGA/PBAC process. At the time of the evaluation, the TGA Round 1 clinical evaluation was available. The TGA round 2 (final) clinical evaluation became available in September 2018. On 31 October 2018 venetoclax in combination with rituximab was added to the ARTG for:
* treatment of adult patients with chronic lymphocytic leukaemia (CLL) who have received at least one prior therapy.
  1. The associated streamlined codependent submission to MSAC to request addition of venetoclax to MBS item number 73343, which currently funds 17p-deletion testing for ibrutinib and idelalisib in relapsed or chronic lymphocytic leukaemia via fluorescence in situ hybridisation (FISH), was scheduled to be considered at the 22-23 November 2018 MSAC meeting.

# Population and disease

* 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. The disease is more common in men than women (65% versus 35%), with a mean age at diagnosis in Australia of 70 years (males 68.8 years, females 71.2 years).
  2. CLL is generally a slowly progressing cancer, with many patients managed with watchful waiting until symptoms develop, and a proportion of patients never requiring treatment. Treatment is typically non-curative, with patients potentially receiving multiple lines of therapy as their disease becomes relapsed/refractory to their current treatment.
  3. The submission positioned venetoclax as a second-line treatment option in patients with relapsed/refractory CLL who are considered unsuitable for treatment or retreatment with a purine analogue.

*For more detail on the PBAC’s view, see Section 7 PBAC Outcome.*

# Comparator

* 1. The submission nominated ibrutinib monotherapy as the main comparator. The PBAC agreed with the submission that ibrutinib is an appropriate comparator. There remained significant uncertainty, however, as to the extent that ibrutinib would be replaced by venetoclax plus rituximab, and potential for sequential use rather than substitution. The PBAC considered it would not be appropriate to limit sequential therapy, particularly as the treatment pathway is still evolving and there was recently published evidence in the Lancet Oncology[[1]](#footnote-1) of durable clinical activity and favourable tolerability of venetoclax use subsequent to ibrutinib.
  2. The submission noted that idelalisib plus rituximab is also PBS-listed for use in patients with relapsed/refractory CLL considered inappropriate for chemoimmunotherapy. However, the submission argued that idelalisib plus rituximab is not a relevant comparator, as available PBS dispensing data suggests that there has been minimal uptake since listing, and expert advice suggests idelalisib plus rituximab is not being used in the second-line relapsed/refractory CLL setting. The evaluation considered idelalisib plus rituximab may be a relevant comparator because its eligible population as defined by its listing overlaps with the requested listing for venetoclax plus rituximab. Therefore, in the context of the cost-minimisation approach taken by the submission, a further consideration for PBAC is that, under Section 101(3B) of the *National Health Act 1953*, when the proposed medicine is substantially more costly than an alternative therapy, the committee cannot make a positive recommendation unless it is satisfied that, for some patients, the proposed medicine provides a significant improvement in efficacy and/or reduction of toxicity over the alternative therapy. If the committee is so satisfied, it must make a statement to this effect. The ESC noted that the submission did not compare the efficacy or toxicity of venetoclax plus rituximab versus idelalisib plus rituximab to help PBAC address Section 101(3B). However, the PBAC considered the time limited course of venetoclax plus rituximab was likely to be a less toxic regimen than idelalisib plus rituximab, given reported fatal adverse events with idelalisib and the TGA boxed warning regarding risk of infection.
  3. The PBAC noted the phase III randomised controlled trial data presented in this submission (MURANO) showed venetoclax plus rituximab was more effective than bendamustine plus rituximab, which included approximately one third of patients in the comparator arm receiving either ibrutinib or idelalisib after disease progression.
  4. The evaluation considered venetoclax monotherapy may also be an appropriate comparator. Venetoclax received positive recommendations at the July and November 2017 PBAC meetings for the treatment of relapsed or refractory CLL in patients who have failed treatment with a kinase inhibitor. The ESC noted that there is no head to head comparison of venetoclax monotherapy vs venetoclax plus rituximab. However venetoclax monotherapy was still not listed on the PBS despite a positive PBAC recommendation, and was cost minimised to idelalisib plus rituximab, rather than to ibrutinib. The ESC noted that, in July and Nov 2017, when the PBAC recommended venetoclax monotherapy based on cost-minimisation to idelalisib plus rituximab, the Committee rejected the request to list venetoclax monotherapy as a second-line treatment option as there was an insufficient basis to justify that venetoclax could substitute for ibrutinib in this population (Venetoclax Public Summary Document, July 2017, p22).

*For more detail on the PBAC’s view, see Section 7 PBAC Outcome.*

# Consideration of the evidence

## Sponsor hearing

* 1. The sponsor requested a hearing for this item. The clinician presented data from the venetoclax clinical trials and provided information regarding the treatment of CLL. In response to the PBAC’s questions, the clinician stated that it would be preferable to be able to access both venetoclax plus rituximab and ibrutinib for use in different patients, and that there would likely be some sequential use. It was also noted that idelalisib is poorly tolerated and would not be the preferred treatment option after progression on ibrutinib.
  2. The PBAC considered the hearing was informative for providing context about the clinical place of venetoclax plus rituximab.

## Consumer comments

* 1. The PBAC noted and welcomed the input from the individual (1), health care professional (1) and organisation (1) received via the Consumer Comments facility on the PBS website. The comments described benefits of treatment with venetoclax including the option of avoiding fludarabine treatment/re-treatment when not clinically appropriate and improvement in quality of life after a loss of response to initial therapies.
  2. The PBAC noted the support received from Lymphoma Australia detailing some of the benefits that could be expected from listing venetoclax for the treatment of CLL, including extending the lives of high-risk patients with chromosomal abnormalities or genetic mutations, and improving quality of life. The PBAC noted that this advice was supportive of the evidence provided in the submission in comparison to bendamustine plus rituximab (MURANO), although the potential benefits in overall survival and quality of life when compared to ibrutinib (the comparator), were not supported.

## Clinical trials

* 1. No head-to-head trials comparing venetoclax plus rituximab to ibrutinib were identified.
  2. The effectiveness claim was based on a multiple step indirect comparison. The first step compared venetoclax plus rituximab (MURANO) to ibrutinib plus bendamustine plus rituximab (HELIOS), using bendamustine plus rituximab as the common reference:
* venetoclax plus rituximab versus bendamustine plus rituximab (MURANO);
* ibrutinib plus bendamustine plus rituximab versus placebo plus bendamustine plus rituximab (HELIOS).
  1. Next, the submission argued that ibrutinib plus bendamustine plus rituximab can be used as a proxy for ibrutinib monotherapy based on Hillmen et al (2015).
  2. The comparator, ibrutinib monotherapy, was listed on the PBS on the basis of the RESONATE trial (ibrutinib vs ofatumumab). To further support the indirect comparison above, the submission presented a matching adjusted indirect comparison (MAIC) of venetoclax plus rituximab (MURANO) to ibrutinib monotherapy (RESONATE) to support the comparative effectiveness claim.
  3. The comparative safety claim was based on the results of a naïve indirect comparison of safety outcomes between venetoclax plus rituximab (MURANO) and ibrutinib monotherapy (RESONATE).

Table 2: Trials and associated reports presented in the submission

|  |  |  |
| --- | --- | --- |
| **Trial ID** | **Protocol title/ Publication title** | **Publication citation** |
| **Venetoclax plus rituximab clinical trials** | | |
| MURANO  (NCT02005471) | A phase three, open-label randomised study of venetoclax plus rituximab compared with bendamustine plus rituximab in relapsed/refractory patients with chronic lymphocytic leukemia | Clinical Study Report,  December 2017. |
| Seymour J, Kipps T, Eichhorst B, et al. Venetoclax–Rituximab in Relapsed or Refractory Chronic Lymphocytic Leukemia. | *New England Journal of Medicine* (2018); 378:1107-20 |
| **Ibrutinib/ibrutinib plus bendamustine plus rituximab clinical trials** | | |
| HELIOS  (NCT01611090) | Chanan-Khan A, Cramer P, Demirkan F, et al. Ibrutinib combined with bendamustine and rituximab compared with placebo, bendamustine, and rituximab for previously treated chronic lymphoblastic leukemia or small lymphocytic lymphoma (HELIOS): a randomised double-blind, phase 3 study. | *Lancet Oncology* (2016); 17(2): 200-211. |
| Cramer P, Fraser G, Santucci-Silva R, et al. Improvement of fatigue, physical functioning, and well-being among patients with severe impairment at baseline receiving ibrutinib in combination with bendamustine and rituximab for relapsed chronic lymphocytic leukemia/small lymphocytic lymphoma in the HELIOS study. | *Leukemia and Lymphoma* (2018); 3:1-10. |
| RESONATE  (NCT01578707) | Byrd JC, Brown JR, O'Brien S, Barrientos JC, Kay NE, Reddy NM, Coutre S, Tam CS, Mulligan SP, Jaeger U, Devereux S. Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia. | *New England Journal of Medicine* (2014); 371(3): 213-223. |
| Brown J, Hillmen P, O’Brien S, et al. Extended follow-up and impact of high-risk prognostic factors from the phase 3 RESONATE study in patients with previously treated CLL/SLL. | *Leukemia* (2018); 32:83-91. |
| Byrd J, Hillmen P, O’Brien S, et al. Long-term efficacy and safety of ibrutinib (Ibr) in previously treated chronic lymphocytic leukemia (CLL): Up to four years follow-up of the RESONATE study. | *Journal of Clinical Oncology* (2017); 35(15):7510. |
| Hillmen, 2015 (Abstract) | Hillmen P, Fraser G, Jones J, et al. Comparing single-agent ibrutinib, bendamustine plus rituximab (BR) and ibrutinib plus BR in patients with previously treated chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL): An indirect comparison of the RESONATE and HELIOS trial. | *Blood* (2015);126(23):2944. |

Source: Table 22, pp49-50; Table 23, pp51-52 of the submission.

* 1. The key features of the direct randomised trials are summarised in the table below.

Table 3: Key features of the included evidence

| **Trial** | **N** | **Design/ duration** | **Risk of bias** | **Patient population** | **Outcomes** |
| --- | --- | --- | --- | --- | --- |
| **Venetoclax plus rituximab versus bendamustine plus rituximab** | | | | | |
| MURANO | 389 | Phase 3, R, OL (median duration of follow-up of 36.0) | Unclear | * Adult patients with relapsed or refractory CLL; * 1 to 3 prior lines of therapy, including at least one standard chemotherapy-containing regimen; * ECOG score ≤1. | * INV-assessed PFS (primary) * IRC-assessed PFS * INV-assessed best OR * IRC- and INV-assessed response * OS * Event-free survival * Proportion with MRD negativity * HRQOL (MDASI, EORTC QLQ-C30 and QLQ-CLL16) |
| **Ibrutinib plus bendamustine plus rituximab versus bendamustine plus rituximab** | | | | | |
| HELIOS | 578 | Phase 3, R, DB, PC  (median duration of follow-up of 25.4 months) | Low | * Adult patients with relapsed or refractory CLL or SLL; * ≥1 prior CLL therapy; * ECOG score ≤1; * Measurable lymph node disease (>1.5 cm) by CT scan. * Excluded patients with 17p deletion. | * IRC-assessed PFS (primary) * INV-assessed PFS * IRC- and INV-assessed ORR * OS * Proportion with MRD negativity * HRQOL (time to improvement in FACIT-Fatigue) |
| **Ibrutinib versus ofatumumab** | | | | | |
| RESONATE | 391 | Phase 3, R, OL  (median duration of follow-up 44 months) | Unclear | * Adult patients considered inappropriate for purine analogue-based treatment; * ≥1 prior CLL therapy; * ECOG ≤1. | * IRC-assessed PFS (primary) * Investigator-assessed PFS * IRC- and INV-assessed ORR * OS * HRQOL (EORTC QLQ-C30, EQ-5D-5L, FACIT-Fatigue). |

DB=double blind; MC=multi-centre; OL=open label; OS=overall survival; PFS=progression-free survival; R=randomised

Source: compiled during the evaluation

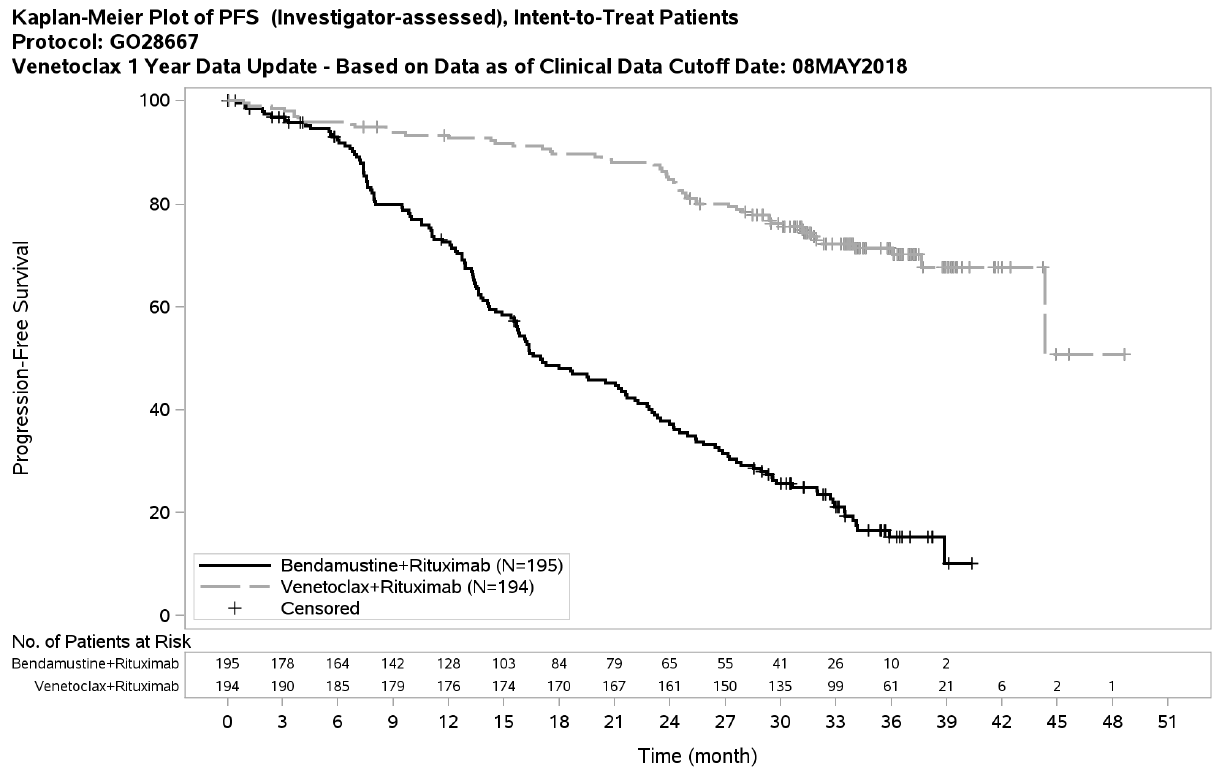
* 1. There were major differences between the included trials in eligibility criteria. While all trials recruited adult patients with relapsed/refractory disease, only the RESONATE trial required patients to be inappropriate for treatment with a purine analogue. The HELIOS trial excluded patients with 17p deletion. The presence of a 17p deletion is predictive of resistance to conventional chemoimmunotherapy regimens, including bendamustine plus rituximab.
  2. There were differences between the trials in patient characteristics, including number of prior therapies, Rai disease stage, and the presence of bulky disease. In general, patients in the RESONATE trial were the most treatment experienced, with the largest number of prior therapies, and more advanced disease. Patient in the MURANO trial were the least treatment experienced, at an earlier Rai disease stage, with a lower proportion of bulky disease (≥5 cm). Higher number of prior treatments and more advanced disease stage may reduce treatment efficacy.

## Comparative effectiveness

### Whole trial population

* 1. Figure 1 presents the Kaplan-Meier plot of investigator-assessed progression free survival for the MURANO trial at the May 2018 data cut.

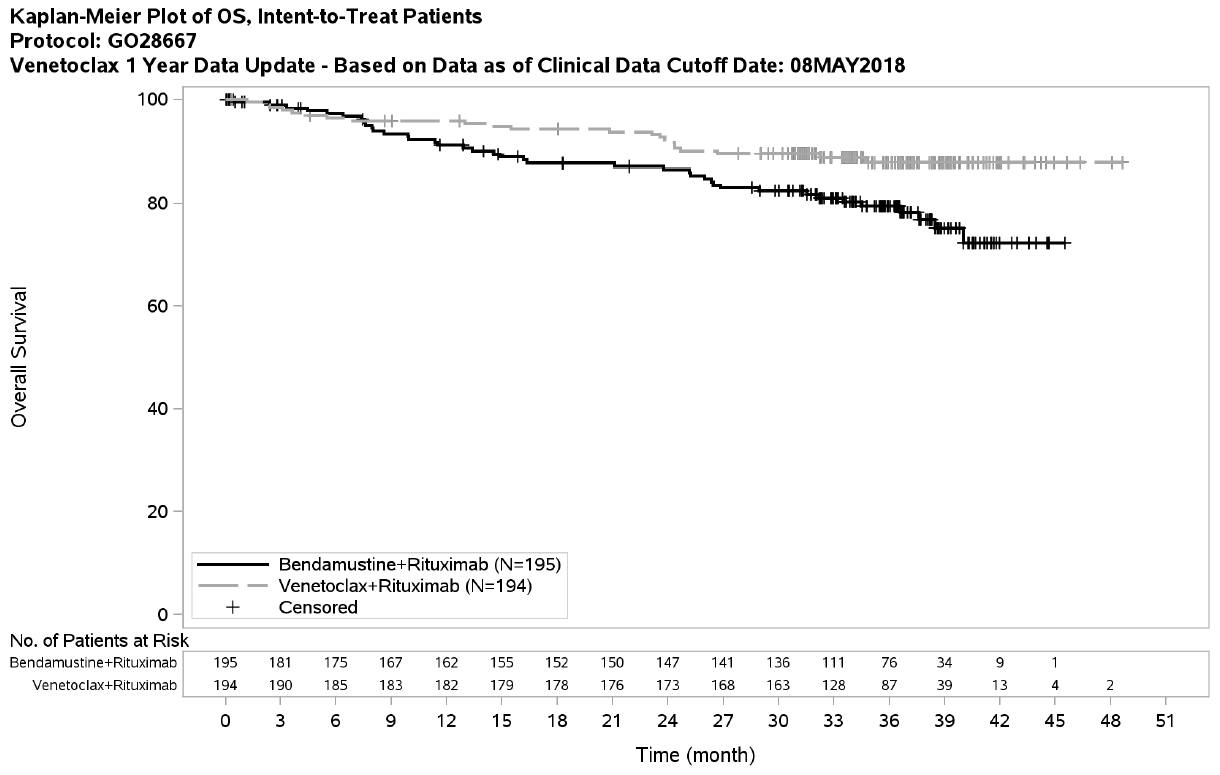
**Figure 1: Investigator-assessed progression-free survival results for the MURANO trial (May 2018 data cut)**



Source: Figure 1, p.3 of the MURANO updated data cut (May 2018).

* 1. At a median duration of follow-up of 36.0 months, venetoclax plus rituximab was associated with a statistically significant improvement in progression-free survival compared to bendamustine plus rituximab (hazard ratio 0.16; 95% CI: 0.12, 0.23). Median progression-free survival was not reached in the venetoclax plus rituximab arm, versus 17.0 months in the bendamustine plus rituximab arm.
  2. Based on the MURANO trial protocol, venetoclax treatment was to be ceased after 25 months of treatment (5-week dose titration plus 24 months). There appears to be a change in the slope of the progression-free survival curve at around this time-point which may represent an increased rate of disease progression associated with discontinuation of venetoclax. There is a large amount of censoring beyond 30 months.
  3. Figure 2 presents the Kaplan-Meier plot of overall survival for the MURANO trial at the May 2018 data cut.

**Figure 2: Overall survival results for the MURANO trial (May 2018 data cut)**



Source: Figure 6, p.9 of the MURANO updated data cut (May 2018).

* 1. At a median duration of follow-up of 36.0 months, venetoclax plus rituximab was associated with a statistically significant improvement in overall survival compared to bendamustine plus rituximab (hazard ratio 0.50; 95% CI: 0.30, 0.85). Median overall survival had not been reached in either treatment group. Longer-term overall survival rates are likely to have been affected by use of other treatments such as ibrutinib following disease progression.

### Subgroup analyses - Proxy PBS subgroup

* 1. The submission acknowledged that the eligibility criteria for the MURANO trial was broader than for the proposed PBS restriction, as eligibility criteria for the MURANO trial did not require patients to be unsuitable for treatment with a purine analogue. To address this difference, the submission derived a proxy PBS subgroup using individual patient data from the MURANO trial.
  2. The proxy PBS subgroup consisted of patients aged over 70 years, or who were stratified as ‘high-risk’ in the MURANO trial due to: presence of 17p deletion; no response to a first-line chemotherapy-containing regimen; or relapse within 12 months of chemotherapy or relapse within 24 months of chemoimmunotherapy. Based on the results of a post-hoc subgroup analysis, the submission estimated that around '''''% of patients in the MURANO trial would meet the eligibility criteria in the proposed restriction.
  3. Treatment with venetoclax plus rituximab in the proxy PBS subgroup was associated with a statistically significant improvement in progression-free survival compared to bendamustine plus rituximab (hazard ratio ''''''''; 95% CI: ''''''''' '''''''''). The results for the overall survival comparison favoured venetoclax plus rituximab, but did not reach statistical significance (hazard ratio '''''''''; 95% CI: '''''''''' ''''''''). The submission claimed that the results for the PBS proxy subgroup were consistent with those for the full trial population. The applicability of the proxy PBS subgroup results to the PBS population is unclear. Patients in the PBS population are likely to be older, more treatment experienced, at a higher disease stage, and with higher rates of fludarabine-refractory disease. Patients in the PBS population may have received prior treatment with ibrutinib or idelalisib plus rituximab. The ESC considered that there was also a risk that the estimate of '''''% of patients with MURANO trial criteria meeting the PBS eligibility criteria was an underestimate because unsuitability for purine analogue treatment is prone to clinician subjectivity, with risk of leakage to a broader population more in keeping with the MURANO trial population.

### Indirect comparison

* 1. The submission conducted an indirect comparison of venetoclax plus rituximab to ibrutinib plus bendamustine plus rituximab, based on the results of the MURANO and HELIOS trials, using bendamustine plus rituximab as the common reference. The indirect comparison was conducted using the Bucher method.
  2. The submission assumed that the ibrutinib plus bendamustine plus rituximab arm of the HELIOS trial could be used as a proxy for the efficacy of ibrutinib monotherapy, based on the results of an analysis by Hillmen et al. (2015). This assumption may be biased against venetoclax plus rituximab, as any additional benefit of adding bendamustine plus rituximab would favour the ibrutinib arm of the indirect comparison. However, it is unknown whether pharmacokinetic or pharmacological interaction between ibrutinib, bendamustine and rituximab could potentially have a negative impact on the efficacy of ibrutinib.
  3. The submission claimed that, despite some differences in the distribution of potential effect modifiers between the trial populations, the patient characteristics of the two trials broadly overlapped, and that an indirect treatment comparison using bendamustine plus rituximab was appropriate. Differences in trial design (open-label in MURANO versus double-blind placebo-controlled in HELIOS) and the distribution of potential treatment effect modifiers between the trial populations limited the exchangeability of the trials. Median progression-free survival was longer for the bendamustine plus rituximab arm of the MURANO trial (17.0 months), compared to the placebo plus bendamustine plus rituximab arm of the HELIOS trial (14.2 months).
  4. Given the reduced efficacy of bendamustine plus rituximab in patients with 17p deletion, the indirect comparison is likely to be biased in favour of venetoclax plus rituximab i.e. the difference between venetoclax plus rituximab and bendamustine plus rituximab in the MURANO trial would be larger than expected in a non-17p deletion population, such as in the HELIOS trial.
  5. Table 4 presents the results for the indirect comparisons of progression-free and overall survival.

**Table 4: Indirect comparison of progression-free survival between the MURANO and HELIOS trials**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **MURANO**  **(N=389)** | **HELIOS**  **(N=578)** | **MURANO**  **VEN + RIT vs.**  **BEN + RIT**  **HR (95% CI)** | **HELIOS**  **IBR + BEN + RIT vs. PBO + BEN + RIT**  **HR (95% CI)** | **Indirect estimate**  **HR (95%CI)** |
| **Median follow-up** | **Median follow-up** |
| **Progression-free survival (investigator-assessed)** | | | | |
| 23.8 months | 25.4 months | 0.17 (0.11, 0.25) | 0.20 (0.15, 0.26) | 0.85 (0.52, 1.40) |
| 36.0 months | 25.4 months | 0.16 (0.12, 0.23) | 0.20 (0.15, 0.26) | 0.80 (0.53, 1.23) |
| **Overall survival** | | | | |
| 23.8 months | 25.4 months | 0.48 (0.25, 0.9) | 0.63 (0.34, 1.02) | 0.76 (0.34, 1.71) |
| 36.0 months | 25.4 months | 0.50 (0.30, 0.85) | 0.63 (0.39, 1.02) | 0.80 (0.39, 1.63) |

Hazard ratio <1 favours venetoclax plus rituximab.

Source: Table 7, p13-14 of the ‘MURANO updated datacut’ Word document provided during the evaluation.

Abbreviations: VEN, venetoclax; RIT, rituximab; BEN, bendamustine; HR, hazard ratio; CI, confidence interval; IBR, ibrutinib; PBO, placebo.

* 1. There were no statistically significant differences between venetoclax plus rituximab and ibrutinib plus bendamustine plus rituximab for progression-free or overall survival, with point estimates favouring venetoclax plus rituximab. No non-inferiority margin was nominated in the submission. The lack of a statistically significant difference is not a robust method for determining non-inferiority, as the wide confidence intervals may not exclude clinically important differences.
  2. The indirect comparison of overall survival results was affected by patient crossover to ibrutinib treatment following disease progression in the HELIOS trial, and patients accessing other treatments, including ibrutinib, following disease progression in the MURANO trial.

### Matching adjusted indirect comparison

* 1. The submission conducted a matching adjusted indirect comparison (MAIC) to support the indirect analysis, using individual patient data from the MURANO trial and the published results of the RESONATE trial. As no common reference arm was available, the submission conducted an unanchored MAIC. The MAIC was unable to adequately match for the number of prior treatments, as the eligibility criteria for the RESONATE trial were broader than the MURANO trial with regard to the number of prior treatments. The ESC considered that the differing trial populations introduced uncertainty into the matching adjusted indirect comparison*.*
  2. For an unanchored indirect comparison, population adjustment methods should adjust for all effect modifiers and prognostic variables (NICE Technical Support Document 18; Phillippo et al. 2016). It was unclear whether all relevant effect modifiers and prognostic variables were identified in the analysis. Some of the prognostic/effect modifier variables identified in the MAIC technical document were not included in the analysis (time from diagnosis, refractory to last anti-leukaemia therapy, and fludarabine refractory). There was insufficient justification provided for the dichotomous variable cut-offs selected for matching (age, Rai disease stage, prior therapies, bulky disease).
  3. In order to match inclusion criteria for RESONATE, patients in the venetoclax plus rituximab arm of the MURANO trial were excluded from further analysis if they had no available central laboratory assessment of 17p deletion status, an ECOG score greater than one, or had received prior B-cell receptor pathway inhibitors. This reduced the number of patients available for matching to 169 (87% of initial sample of 194 patients). Matching for the selected variables resulted in an effective sample size of 62 patients. The large reduction in effective sample size is likely due to limited overlap between the trial populations. Post-matching patient characteristics for matched and unmatched variables were not provided.
  4. Figure 3 presents a comparison of Kaplan-Meier progression-free survival curves for the MURANO (adjusted and unadjusted) and RESONATE trials. A comparison of results for overall survival is presented in Figure 4.

Figure 3: Kaplan-Meier curves for the MAIC of investigator-assessed progression-free survival



Source: Figure 8, p.48 of the MAIC technical document, Attachment 6 of the submission.

Abbreviations: PFS, progression-free survival; VEN, venetoclax; R, rituximab; Unadj, unadjusted; BR, bendamustine plus rituximab; IBR, ibrutinib; OFA ofatumumab; Adj, adjusted.

Figure 4: Kaplan-Meier curves for the MAIC of overall survival



Source: Figure 8, p.48 of the MAIC technical document, Attachment 6 of the submission.

Abbreviations: OS, overall survival; VEN, venetoclax; R, rituximab; Unadj, unadjusted; BR, bendamustine plus rituximab; IBR, ibrutinib; OFA ofatumumab; Adj, adjusted.

* 1. Table 5 presents the results of the MAIC of progression-free survival and overall survival.

Table 5: Results of the matching adjusted indirect comparison for progression-free survival and overall survival

|  |  |  |  |
| --- | --- | --- | --- |
| Outcome | MURANO  VEN + RIT  HR (95% CI) | RESONATE  IBR vs OFA  HR (95% CI) | VEN + RIT vs IBR  HR (95% CI) |
| **Progression-free survival** | | | |
| Unadjusted | '''''''''''''' ''''''''''''''''' ''''''''''''' | ''''''''''''''' ''''''''''''''' '''''''''''''' | ''''''''''''' ''''''''''''''''' ''''''''''''''' |
| Adjusted | '''''''''''''' '''''''''''''''''' ''''''''''''''' | '''''''''''''' '''''''''''''''''' '''''''''''''''' | '''''''''''''' '''''''''''''''''' '''''''''''''''' |
| **Overall survival** | | | |
| Unadjusted | '''''''''''''' '''''''''''''''''' ''''''''''''''' | '''''''''''' '''''''''''''''' '''''''''''''''' | ''''''''''''' ''''''''''''''''' '''''''''''''''' |
| Adjusted | ''''''''''''' ''''''''''''''''' ''''''''''''''' | '''''''''''' '''''''''''''''''' '''''''''''''''' | ''''''''''''' '''''''''''''''''' '''''''''''''''' |

Hazard ratio <1 favours venetoclax plus rituximab.

Source: Table 15, p.50 of MAIC technical document, Attachment 6 of the submission.

Abbreviations: VEN, venetoclax; RIT, rituximab; IBR, ibrutinib; HR, hazard ratio; CI, confidence interval.

* 1. Based on the adjusted results, there was a statistically significant difference for overall survival (in favour of venetoclax plus rituximab), but no statistically significant difference in progression-free survival. Adjustment in the MAIC had a large impact on the venetoclax plus rituximab results, particularly for the overall survival outcome. The results of the unanchored MAIC were considered to be highly uncertain, and at very high risk of bias.

## Comparative harms

* 1. The claim of non-inferior safety was based on a naïve indirect comparison of safety results for venetoclax plus rituximab (MURANO) and ibrutinib (RESONATE), summarised in the table below.

Table 6: Naïve indirect comparison of safety outcomes between venetoclax plus rituximab and ibrutinib

|  | **MURANO**  **VEN + RIT**  **N=194** | | **RESONATE**  **IBR**  **N=195** | | |
| --- | --- | --- | --- | --- | --- |
| Median duration of follow-up, months (range) | May 2017 cut  24.8 (0.3-37.4) | May 2018 cut  36.1 (0.3-48.6) | Byrd 2014  9.4 (0.1-16.6) | Brown 2018  19 (NR) | Byrd 2017  44 (NR) |
| Grade 3 or 4 AE | 159 (82.0) | ''''''''' '''''''''''''' | 99 (51) | NR | NR |
| Serious AE | 90 (46.4) | ''''''' ''''''''''''' | 81 (42) | NR | NR |
| Treatment-related AE | 170 (87.6) | ''''''''' ''''''''''''''' | NR | NR | NR |
| Discontinuations due to AE | 30 (15.5) | '''''' ''''''''''''''' | 8 (4.1) | NR | 23 (11.8) |
| AE leading to death | 10 (5.2) | ''''' ''''''''''' | 8 (4) | NR | NR |
| Any AE | 194 (100) | ''''''''' '''''''''''' | 194 (99) | NR | NR |
| Any grade, incidence ≥20%:   * Neutropenia * Anaemia * Diarrhoea * Nausea * Upper respiratory tract infection * Fatigue * Pyrexia * Cough | 118 (61)  30 (16)  77 (40)  41 (21)  43 (22)  34 (18)  29 (15)  35 (18) | '''''''''  ''''''''  ''''''''  '''''''''  '''''''  '''''''''  '''''''''  ''''''''' | 42 (22)  44 (23)  93 (48)  51 (26)  31 (16)  54 (28)  46 (24)  38 (20) | 50 (26)  49 (25)  105 (54)  61 (31)  49 (25)  67 (34)  58 (30)  51 (26) | NR  NR  NR  NR  NR  NR  NR  NR |
| Grade ≥3, incidence ≥5%:  Neutropenia  Anaemia  Thrombocytopenia  Febrile neutropenia  Pneumonia  Neutrophil count decreased  Diarrhoea  Major haemorrhage  Atrial fibrillation | 112 (58)  21 (11)  11 (6)  7 (4)  10 (5)  10 (5)  5 (3)  0  1 (<1) | ''''''''' '''''''''  ''''' ''''''''''  '''''' ''''''''  ''''''' ''''''''  '''''' '''''''  '''''' '''''''  ''' ''''''  '''  ''' ''''''''''' | 32 (16)  9 (5)  11 (6)  NR  13 (7)  NR  8 (4)  NR  7 (NR) | 38 (20)  12 (6)  11 (6)  NR  20 (10)  NR  9 (5)  NR  NR | NR (23)  NR (8)  NR (8)  NR  NR (17)  NR  NR (6)  12 (6)  11 (6) |

Source: Table 42, p.107; Table 43, pp108-109; Table 44, pp110-11 of the submission; Table 11, p.17 of the ‘MURANO updated datacut’ Word document provided during the evaluation; Table 2, p.220 of Byrd et al. (2014); Table 3, p.88 of Brown et al. (2018); Byrd et al. (2017) conference poster.

* 1. Reported rates of Grade 3/4 adverse events were numerically higher for venetoclax plus rituximab compared with ibrutinib, predominantly due to higher rates of neutropenia and anaemia. The ESC considered that this difference is likely to be clinically relevant, especially for the PBS population who are likely to be older and have more comorbidities. Discontinuations due to adverse events were also numerically higher for venetoclax plus rituximab. The results of the naïve indirect safety comparison should be interpreted with caution, given differences in the trial populations and differences in the timing of assessments.

## Clinical claim

* 1. The submission described venetoclax plus rituximab as non-inferior in terms of effectiveness, and different, but non-inferior, in terms of safety compared to ibrutinib monotherapy.
  2. The following issues with the clinical claim presented in the submission were identified in the evaluation:
  + The claim of non-inferior effectiveness was based on an indirect comparison of venetoclax plus rituximab (MURANO) to ibrutinib plus bendamustine plus rituximab (HELIOS) using bendamustine plus rituximab as common reference. The indirect comparison relied upon the assumption that ibrutinib plus bendamustine plus rituximab was a suitable proxy for ibrutinib monotherapy.
  + Differences in trial design and the distribution of potential treatment effect modifiers between the MURANO and HELIOS trials limited the exchangeability of the trials. Given the reduced efficacy of bendamustine plus rituximab in patients with 17p deletion, the indirect comparison was likely to be biased in favour of venetoclax plus rituximab.
  + The submission presented an unanchored MAIC of venetoclax plus rituximab (MURANO) and ibrutinib (RESONATE) to support the indirect comparison. It was unclear whether all relevant effect modifiers and prognostic variables were identified and included in the analysis. Matching for the selected variables resulted in a large reduction in effective sample size, likely due to limited overlap between the trial populations. The results of the unanchored MAIC were considered to be highly uncertain, and at very high risk of bias.
  1. The ESC considered the multiple step indirect comparison resulted in a high level of uncertainty in deeming non-inferior effectiveness of venetoclax plus rituximab versus ibrutinib; however, the MURANO trial data does support clinical efficacy of venetoclax plus rituximab and its place of therapy is likely to be similar to that of ibrutinib, albeit venetoclax plus rituximab sequential therapy may occur after ibrutinib. The proposed place of venetoclax plus rituximab in the management of CLL is supported by treatment guidelines.
  2. The claim of non-inferior safety was based on a naïve indirect comparison of safety results for venetoclax plus rituximab (MURANO) and ibrutinib (RESONATE). Overall, this claim may not be adequately supported due to a lack of available comparative data. Reported rates of Grade 3/4 adverse events were numerically higher for venetoclax plus rituximab, predominantly due to higher rates of neutropenia and anaemia. The ESC considered there was uncertainty with the naïve indirect comparison; however, the greater rate of Grade 3 and 4 adverse events after venetoclax plus rituximab were likely to be clinically relevant. Non-inferior safety therefore is doubtful and the ESC agreed with the evaluation that this claim is not adequately supported. As a consequence, additional treatment costs for adverse events should be incorporated in the cost-minimisation analysis. The Pre-PBAC Response included a breakdown of the costs of AEs, noting that as ibrutinib is administered until disease progression, this cost was likely to be underestimated for ibrutinib as patients may continue to experience AEs whilst they are on active treatment.
  3. The PBAC considered that the claim of non-inferior comparative effectiveness versus ibrutinib was reasonable.
  4. The PBAC considered that the claim of non-inferior comparative safety was uncertain given the greater rate of Grade 3 and 4 adverse events with venetoclax plus rituximab was likely to be clinically relevant and that a claim of a different safety profile was more accurate.

*For more detail on the PBAC’s view, see Section 7 PBAC Outcome.*

## Economic analysis

* 1. The submission presented a cost-minimisation analysis of venetoclax plus rituximab versus ibrutinib, based on the claim of non-inferior effectiveness and different but non-inferior safety. Should the PBAC accept the clinical claim of overall non-inferior effectiveness and safety, the cost-minimisation approach must establish that the cost per patient for treatment with venetoclax plus rituximab would be no more than the cost per patient of ibrutinib monotherapy. The cost per patient takes into account the mean equi-effective doses of the new intervention and the alternative therapy, and also accounts for any difference in the mean duration of treatment. Where these cost per patient calculations are uncertain, the guiding principle is that the Australian Government should not bear the financial risk of this uncertainty because the Australian population already has access to therapy that is at least as effective and safe.
  2. The cost-minimisation analysis incorporated different treatment durations for venetoclax and ibrutinib. The recommended treatment course for venetoclax was based on the indication proposed in the draft product information (24 months plus 5-week titration). However, the assumed treatment duration is associated with uncertainty, given the limited long-term follow-up of patients in the post-treatment phase. There is potential for venetoclax to be used for longer than 24 months if longer-term efficacy data does not demonstrate durability of treatment effect in the post-treatment period. The Pre-Sub-Committee Response (PSCR) argued the product information and proposed PBS restriction include criteria to prevent treatment for longer than 24 months after the 5-week titration period. The ESC advised the potential uncertainty in treatment duration due to the limited long-term efficacy data should also be managed through a risk sharing agreement (RSA), and by calculation of the treatment cost per patient for venetoclax plus rituximab being ''''' ''''''''''' '''''''''' the cost per patient of ibrutinib monotherapy.
  3. The submission assumed a maximum treatment duration for ibrutinib of 44 months based on the median duration of follow-up for ibrutinib reported in the most recent publication for the RESONATE trial (compared to 72 months in the financial estimates). The assumption of a 44-month maximum treatment duration may not be reasonable, as some patients will require treatment for more than 44 months. The estimate of treatment duration for ibrutinib has a large impact on the cost-minimised price for venetoclax. The ESC advised that the cost-minimisation approach would need to be based on the treatment duration of ibrutinib accepted to obtain its PBS listing. There is risk of longer treatment duration with both venetoclax (see paragraph 6.3) and ibrutinib. As a result, venetoclax plus rituximab, if PBAC recommended, would need to ''''''' '''''' ''''''''''''''''' ''''''''.
  4. The submission used the ibrutinib progression free survival curve from the RESONATE trial to adjust for the proportion of patients who discontinue treatment due to disease progression. The submission claimed that the use of a single progression-free survival curve was consistent with the claim of non-inferior efficacy, and the assumption that venetoclax plus rituximab and ibrutinib patients experience the same rate of disease progression. Treatment discontinuations for reasons other than disease progression, such as adverse events, were not included in the analysis. This may not be reasonable given potential differences in adverse event profiles and tolerability between treatments. The analysis did not adjust for differences in dose intensity between treatments.
  5. Based on the ibrutinib progression-free survival curve, the average time on treatment was estimated to be ''''''''' months for venetoclax and 32.8 months for ibrutinib. The submission claimed that the estimated time on venetoclax derived using the RESONATE progression-free survival curve was consistent with the median venetoclax treatment exposure of 22.1 months observed in the MURANO trial. Based on the May 2018 data cut, median duration of venetoclax exposure was '''''''' months (mean ''''' months).
  6. Based on the recommended treatment course, adjusted for disease progressions, the submission proposed the following equi-effective doses:
* One starting pack and ''''''''''' continuing packs of venetoclax plus 5.80 infusions of rituximab is equi-effective to '''''''''' packs of ibrutinib.
  1. The cost-minimisation analysis included costs associated with administration of rituximab, and costs associated with tumour lysis syndrome prophylaxis. Costs of treating adverse event occurrences were not included in the cost-minimisation analysis. Increased rates of neutropenia associated with venetoclax plus rituximab treatment may result in increased use of granulocyte-colony stimulating factor. Given the greater rate of Grade 3 and 4 adverse events with venetoclax plus rituximab, additional treatment costs of these events, in particular use of growth factor support and treatment of severe tumour lysis and infections, should be incorporated in the cost minimisation approach. The Pre-PBAC Response included the estimated average AE cost for a patient receiving a course of venetoclax plus rituximab treatment based on 36-month follow-up data from MURANO with patients off treatment for an average of 12 months ($''''''') and a patient receiving ibrutinib treatment based on 44-months follow-up from the RESONATE trial ($''''''') (see table below). The response further suggested that, as ibrutinib is administered until disease progression, this is likely to underestimate the cost for ibrutinib as patients may continue to experience AEs whilst they are on active treatment.

Table 7: Estimated cost of treating AEs for venetoclax plus rituximab and ibrutinib

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **AE** | **Cost per AE** | **Frequency (VR)** | **Frequency (IBR)** | **WAC\* (VR)** | **WAC\* (IBR)** |
| Clinical TLS | ''''''''''''''''''''' | '''''''''''''' | ''''''''''''''' | ''''''''' | '''''' |
| Neutropenia (treated) | ''''''''''''''' | ''''''''''''''''''' | '''''''''''''''''' | ''''''''''' | ''''''''''''' |
| AF (Grade 3-4) | ''''''''''''''''' | '''''''''''''''' | '''''''''''''' | '''''''''' | ''''''''''' |
| **Total** |  |  |  | **'''''''''''** | **''''''''''** |

AE: adverse event; VR: venetoclax+rituximab; IBR: ibrutinib; TLS: tumour lysis syndrome; AF: atrial fibrillation; WAC: weighted average cost/patient

Source: Pre-PBAC Response, p3.

* 1. The cost-minimisation was based on the published price of ibrutinib. The analysis was conducted using dispensed price for maximum quantities (DPMQs), rather than ex-manufacturer prices (AEMPs).
  2. Table 8 presents the derivation of the venetoclax DPMQ.

Table 8: Cost-minimised price for venetoclax based on the ibrutinib published price

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Parameter** | **Starting pack** | **Continuing pack** | **10 mg dose hold pack** | **50 mg dose hold pack** |
| Milligrams per pack | 2,590 mg | 12,000 mg | 140 mg | 350 mg |
| Venetoclax price per mg | ''''''''''''' | | | |
| Venetoclax AEMP per pack | ''''''''''''''''''''''' | '''''''''''''''''''''''''' | '''''''''''''''''''' | '''''''''''''''''''' |
| Venetoclax DPMQ per pack | ''''''''''''''''''''''' | ''''''''''''''''''''''''''' | '''''''''''''''''''''' | '''''''''''''''''''' |

Source: Table 68, p.154 of the submission.

AEMP, approved ex-manufacturer price; DPMQ, dispensed price for maximum quantity.

* 1. The submission calculated a DPMQ of $''''''''''' for each venetoclax starting pack, and a DPMQ of $''''''''''''' for each venetoclax continuing pack. The submission acknowledged that the results of the cost-minimisation analysis were uncertain as the effective price of ibrutinib was unknown, and due to assumptions relating to the maximum treatment duration applied to ibrutinib. The ESC considered the cost-minimisation method used to calculate the AEMP and DPMQ of venetoclax was overly complicated. The treatment course cost of venetoclax plus rituximab should equate to the treatment ''''''' ''''''''''''' ''''' '''''''''''''' calculated for its PBS listing, recognising that there will be differences in the published treatment cost course of ibrutinib to the undisclosed treatment cost course. Furthermore, the RSA arrangement in place may further affect the ibrutinib cost, and thus venetoclax plus rituximab would need to join the same RSA to ensure financial risk to the Australian Government is mitigated.

## Drug cost/patient/course: $''''''''''''' (published price)

* 1. Based on the cost-minimisation analysis presented in the submission (adjusted for disease progression using the progression-free survival curve for the ibrutinib arm of the RESONATE trial), the cost per patient per course for venetoclax plus rituximab is $''''''''''''''. The calculation includes one venetoclax starting pack (requested DPMQ of $''''''''''''''''), 20.78 venetoclax continuing packs (requested DPMQ of $'''''''''''''''''), rituximab drug costs of $''''''''''''''''', rituximab administration costs of $''''''''''''', and tumour lysis syndrome prophylaxis costs of $''''''''''''''''', and assumes a maximum treatment duration of 25 months. Given the uncertainty of non-inferior safety of venetoclax plus rituximab versus ibrutinib, the ESC advised that the cost-minimisation be adjusted to incorporate higher adverse event treatment costs.
  2. Based on the cost-minimisation analysis presented in the submission (adjusted for disease progression using the progression-free survival curve for the ibrutinib arm of the RESONATE trial), the cost per patient per course for ibrutinib is $281,130.54. The calculation includes 32.01 ibrutinib packs (DPMQ $8,782.81), and assumes a maximum treatment duration of 44 months. See above comments regarding appropriate method of cost-minimisation.

## Estimated PBS usage & financial implications

* 1. This submission was not considered by DUSC.
  2. TheESC noted the budget impact of patients using venetoclax plus rituximab following ibrutinib, or ibrutinib following venetoclax plus rituximab was not explored in the submission.
  3. The submission used an epidemiological approach to estimate the utilisation and financial implications associated with the PBS listing of venetoclax plus rituximab, due to limited available PBS dispensing data for ibrutinib. Estimates presented in the submission were based on published prices.
  4. The estimated patient numbers were informed by the results of two clinician surveys conducted by the sponsor. An initial survey was conducted in July 2016 to inform the estimates for the venetoclax monotherapy submission. An additional survey of nine Australian consultants specialising in the treatment of CLL was conducted between April and June 2018.
  5. Expected medicine utilisation was adjusted by applying the time-on-treatment curve for the ibrutinib arm of the RESONATE trial to the recommended treatment courses for venetoclax plus rituximab, and ibrutinib. The submission stated that the time-on-treatment curve was chosen (rather than the projected progression-free survival curve which was used in the cost-minimisation analysis) as it accounts for treatment discontinuations, and is more reflective of real world use.
  6. In the budget impact analysis, ibrutinib treatment was assumed to continue for up to 72 months (compared to 44 months in the cost-minimisation analysis). The recommended treatment course for venetoclax was based on the indication proposed in the draft product information. There is potential for venetoclax to be used for longer than 24 months if longer-term efficacy data does not demonstrate durability of treatment effect in the post-treatment period. The longer treatment duration of ibrutinib used in the budget impact analysis is likely to have overestimated the cost offsets for venetoclax.
  7. Table 9 presents the estimated utilisation and financial implications of venetoclax plus rituximab over the first six years of listing.

Table 9: Estimated financial implications for the health budget

|  | **Year 1**  **(2019)** | **Year 2**  **(2020)** | **Year 3 (2021)** | **Year 4**  **(2022)** | **Year 5**  **(2023)** | **Year 6**  **(2024)** |
| --- | --- | --- | --- | --- | --- | --- |
| **Incident CLL patients** | | | | | | |
| Australian population | 25,619,895 | 26,037,356 | 26,452,147 | 26,866,209 | 27,279,046 | 27,690,209 |
| Incidence of CLL (0.0054%) | 1383 | 1406 | 1428 | 1451 | 1473 | 1495 |
| Total treated patients (first-line) | ''''''''' | '''''''''' | '''''''''' | '''''''''' | ''''''''' | '''''''''' |
| Total eligible patients (R/R & not suitable for purine analogue) | '''''''''' | ''''''''' | '''''''''' | '''''''''' | ''''''''' | '''''''''' |
| **Number of packs for VEN + RIT** | | | | | | |
| Venetoclax plus rituximab market share | '''''''''' | '''''''''' | ''''''''''' | '''''''''' | ''''''''''' | ''''''''''' |
| Starting packs | ''''''''' | ''''''''' | ''''''''' | '''''''''' | '''''''''' | ''''''''' |
| Dose-hold packs (10 mg) | ''' | ''' | '''' | ''' | ''' | '''' |
| Dose-hold packs (50 mg) | ''' | ''' | '''' | ''' | ''' | '''' |
| Total continuing packs | ''''''''''''' | ''''''''''''' | '''''''''''' | ''''''''''' | ''''''''''' | ''''''''''''' |
| Rituximab 375mg/m2 | '''''''''' | '''''''''' | ''''''''' | '''''''''' | ''''''''' | ''''''''' |
| Rituximab 500mg/m2 | ''''''''' | ''''''''' | '''''''''' | '''''''''' | ''''''''' | '''''''' |
| **Cost of VEN + RIT** | | | | | | |
| Venetoclax costs | $'''''''''''''''''''''''' | $''''''''''''''''''''''''' | $''''''''''''''''''''''''''''' | $'''''''''''''''''''''''''' | $'''''''''''''''''''''''''''' | $'''''''''''''''''''''''''''' |
| Rituximab costs | $'''''''''''''''''''''' | $'''''''''''''''''''''''''' | $'''''''''''''''''''''''' | $'''''''''''''''''''''''' | $'''''''''''''''''''''' | $'''''''''''''''''''''' |
| Total cost of VEN + RIT | $'''''''''''''''''''''''''' | $'''''''''''''''''''''''''' | $''''''''''''''''''''''''''''' | $''''''''''''''''''''''''''''' | $'''''''''''''''''''''''' | $'''''''''''''''''''''''' |
| Patient copayments ($14.59 per script) | $''''''''''''''' | $''''''''''''''''' | $''''''''''''''''' | $'''''''''''''''''' | $'''''''''''''''' | $''''''''''''''''' |
| Net cost to PBS/RPBS | $'''''''''''''''''''''''''''' | $''''''''''''''''''''''''''''' | $'''''''''''''''''''''''' | $'''''''''''''''''''''''' | $''''''''''''''''''''''''''''' | $''''''''''''''''''''''' |
| **Reduction in IBR cost with VEN + RIT listing** | | | | | | |
| Ibrutinib packs (50% reduction) | '''''''''''' | '''''''''''' | ''''''''''' | ''''''''''' | '''''''''''' | ''''''''''''' |
| Net cost to PBS/RPBS | $'''''''''''''''''''''''''' | $''''''''''''''''''''''''' | $''''''''''''''''''''''''' | $'''''''''''''''''''''''' | $''''''''''''''''''''''''''' | $'''''''''''''''''''''''''' |
| **Additional cost for allopurinol with VEN + RIT listing** | | | | | | |
| Patients initiating VEN + RIT | ''''''''' | '''''''' | '''''''''' | ''''''''' | '''''''''' | ''''''''' |
| Net cost to PBS/RPBS | $'''''''''''' | $''''''''''''' | $'''''''''''''' | $'''''''''''' | $'''''''''''' | $''''''''''''' |
| **Net cost to the PBS/RPBS** | **$''''''''''''''''''** | **$''''''''''''''''''''''** | **$''''''''''''''''''** | **-$'''''''''''''''''''** | **-$'''''''''''''''''''** | **-$''''''''''''''''''''** |

Source: ‘Section 4 VR PBAC July 2018\_1’ Excel workbook of the submission.

Abbreviations: CLL, chronic lymphocytic leukaemia; VEN, venetoclax; RIT, rituximab; IBR, ibrutinib; TLS, tumour lysis syndrome; RIT, rituximab.

*The redacted table shows that at Year 6, the estimated number of patients was less than 10,000 per year and the net saving to the PBS would be $10 – $20 million per year.*

* 1. The submission estimated a net cost to the PBS of less than $10 million to $10 – $20 million per year in Years 1 to 3, and net cost savings of less than $10 million to $10 – $20 million per year in Years 4 to 6. The estimated cumulative net cost over six years was less than $10 million. Net costs in Years 1 to 3 were due to higher annual treatment costs for venetoclax plus rituximab compared to ibrutinib i.e. the cost of 20.78 continuing packs of venetoclax plus 5.80 infusions of rituximab costing the equivalent of 32.01 packs of ibrutinib. Net savings in Years 4 to 6 were driven by the longer duration of treatment with ibrutinib compared to venetoclax.
  2. The utilisation/financial estimates were considered to be highly uncertain due to the following issues:
* The estimates were derived using an incidence-based approach that did not account for prevalent patients who may require treatment.
* Patients currently receiving ibrutinib treatment were not included in the budget impact analysis, however, may be treated with venetoclax plus rituximab as a later-line therapy. The PSCR suggested that these prevalent patients are unlikely to be treated with venetoclax plus rituximab, however the ESC advised that, with the risk of sequential therapy, the numbers of patients treated with venetoclax plus rituximab may be underestimated.
* The derivation of the eligible incident population relied upon the results of two clinician surveys conducted by the sponsor. It was unclear whether the utilisation estimates were reliable due to a potential lack of representativeness, and the currency of the results in a rapidly changing disease area.
* The budget impact analysis did not include idelalisib plus rituximab as a treatment option, despite overlapping PBS restriction criteria.
* It is unclear whether venetoclax plus rituximab will substitute for ibrutinib or be used as a later line therapy, as the optimal sequencing of therapies in this population is not yet established.
* The financial implications did not account for later-line treatments among patients who experience disease progression or discontinue due to adverse events. Venetoclax plus rituximab, ibrutinib, and idelalisib plus rituximab are all potential later-line treatment options. There is also potential for patients treated with venetoclax plus rituximab to be retreated if they experience relapse in the post-treatment period.
* There is limited post-treatment follow-up for venetoclax plus rituximab. There is potential for venetoclax to be used for longer than 24 months if longer-term efficacy data does not demonstrate durability of treatment effect in the post-treatment period.
* There is potential for use of venetoclax outside of the proposed restriction, including use beyond the 24 months, retreatment of patients who experience disease progression, use in the first-line setting (particularly for patients with 17p deletion/TP53 mutation), use of venetoclax as monotherapy, or use in combination with other agents.
  1. The ESC agreed with the evaluation that there are multiple uncertainties associated with the utilisation/financial estimates and advised that, in order to mitigate risk, venetoclax plus rituximab would need to ''''''' '''''' ''''''''''''''' '''''''' '''' ''''''''' for ibrutinib to ensure no net financial cost to government. The PBAC also noted the Pre-PBAC Response indicated sequential use of ibrutinib and venetoclax plus rituximab could result in a substantial increase in the treated patient population. These estimates were not independently evaluated.

## Quality use of medicines

* 1. 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

* 1. The submission acknowledged that ibrutinib is subject to a special pricing arrangement. The submission also noted that ibrutinib is subject to an RSA, but that no details of the agreement are available. The submission stated that the sponsor would work with the Department of Health, should an RSA for venetoclax plus rituximab be required. The PBAC advised that venetoclax plus rituximab would need to '''''''' ''''''' '''''''''''''''' '''''''' '''' '''''''''' '''''' '''''''''''''''''

# PBAC outcome

* 1. The PBAC recommended the listing of venetoclax in combination with rituximab for the treatment of certain patients with relapsed or refractory CLL. The PBAC recommended listing on a cost-minimisation basis with ibrutinib on the basis of equivalent treatment cost per patient, and inclusion in the '''''''''''''' '''''' ''''''''''''''' ''''''''''''''''''' '''''''''' '''''' ''''''''''''''' '''''''' '''''' '''''''''''''' ''''' '''''' ''''''''''''' '''''''''''''''''''''' '''''''''.
  2. The PBAC advised that the sequential use of venetoclax plus rituximab and ibrutinib was likely and may be clinically appropriate given the different mechanism of action and the emerging evidence of clinical benefit with sequential therapy. The PBAC also noted the clinician in the sponsor hearing supported sequential therapy, with the optimal order of sequencing still being unclear. However, the appropriate comparator to a sequential treatment algorithm was unclear, and the submission did not address the likelihood of sequential use. Based on further information on estimated patient numbers provided in the Pre-PBAC Response, the PBAC considered the financial implications of this sequential use could be high, but were also highly uncertain.
  3. The PBAC noted the Pre-PBAC Response requested that sequential use of venetoclax and ibrutinib be excluded from their restriction criteria unless a modified RSA was negotiated to account for the expected additional cost. The PBAC considered it would not be clinically appropriate to restrict sequential use, but the cost-effectiveness of sequential use was uncertain. Therefore, the PBAC recommended venetoclax be listed with the same restriction criteria as ibrutinib and that the requested listing of venetoclax be included in the ''''''''''''' ''''''''''''''' ''''''' ''''''''' ''''' ''''''''''''' '''' '''''' '''''''''''' '''''''''''''''''''' ''''''''''
  4. The PBAC noted the comparator selection issues detailed in section 5 above, and considered ibrutinib was the appropriate comparator (in the second-line treatment setting). The Committee considered this in the context that, for some patients, venetoclax plus rituximab would provide reduced toxicity over idelalisib plus rituximab.
  5. The PBAC recalled its July 2017 recommendation that, based on the limited evidence available at the time, venetoclax was likely to be clinically non-inferior to idelalisib plus rituximab after failure of a kinase inhibitor in relapsed or refractory CLL. The PBAC considered this recommendation in a later setting was based on lower quality evidence (single-arm studies) in a different clinical setting compared to the evidence considered in this submission (a randomised controlled trial in the second-line setting). Additionally, while no formal comparison was conducted during the evaluation, the PBAC considered the time limited venetoclax plus rituximab regimen was likely to be less toxic than idelalisib plus rituximab. Therefore, the PBAC was satisfied overall that venetoclax plus rituximab provides, for some patients, a significant improvement in toxicity over idelalisib plus rituximab.
  6. The PBAC accepted the evidence from the MURANO trial showed venetoclax plus rituximab was more effective than bendamustine plus rituximab, which included approximately one third of patients in the comparator arm receiving either ibrutinib or idelalisib after disease progression. At a median duration of follow-up of 36 months, venetoclax plus rituximab was associated with a statistically significant improvement in investigator-assessed progression-free survival compared to bendamustine plus rituximab (hazard ratio 0.16; 95% CI: 0.12, 0.23) and overall survival (hazard ratio 0.50; 95% CI: 0.30, 0.85).
  7. The PBAC considered the multiple step indirect comparison presented resulted in a high level of uncertainty in supporting the claim of non-inferior effectiveness and safety of venetoclax plus rituximab versus ibrutinib. However, the PBAC accepted the evidence, while uncertain, supported a claim of non-inferior comparative effectiveness. The PBAC considered venetoclax plus rituximab had a different but non-inferior safety profile to ibrutinib, and that the different treatment costs for these adverse event profiles should be incorporated in the cost-minimisation approach.
  8. The PBAC advised that the cost-minimisation approach must establish that the cost per patient for treatment with venetoclax plus rituximab would be no more than the effective cost per patient as already agreed for ibrutinib. The PBAC agreed with the ESC (paragraph 6.51) that the cost-minimisation method used in the submission was overly complicated. The PBAC therefore advised that a more appropriate cost-minimisation approach would need to be based on the treatment duration of ibrutinib which was accepted at the time of its initial PBS listing and include the dose intensity of each medicine. The cost per patient for venetoclax plus rituximab should take into account the infusion costs of administering rituximab. The PBAC considered the treatment costs of adverse events for venetoclax plus rituximab should also be included in the cost per patient calculation, in particular use of growth factor support and the treatment of severe tumour lysis (see Table 7 above).
  9. The PBAC noted there were considerable uncertainties regarding the financial estimates provided in the submission and the estimated patient numbers in the Pre-PBAC Response raised concerns about large increases in costs which were not specifically supported by clinical evidence or economic evaluation. Given these uncertainties and concerns, the PBAC considered that the requested listing of venetoclax would need to ''''''' ''''''' ''''''''''''' ''''''' '''' ''''''''''' ''''' ''''''''''''''' to ensure no net financial cost to the government.
  10. The PBAC advised that a major submission would be required to '''''''''''''''' ''''''' '''''''''''' ''''''''''''''''''''' '''''''' associated with the existing ibrutinib RSA to account for sequential use of these listings.
  11. The PBAC advised that any early access program should accord with the proposed PBS restriction rather than the TGA approval to allow patients to be eligible for grandfathering to the PBS. If the sponsor commits to the early access program, it was requested that a grandfathering restriction be drafted by the sponsor.
  12. The PBAC considered a telephone authority, consistent with the PBS listing of ibrutinib, would be appropriate.
  13. The PBAC advised that venetoclax is not suitable for prescribing by nurse practitioners.
  14. 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.
  15. The PBAC recommended that the Early Supply Rule should apply.
  16. The PBAC noted that this submission was not eligible for an Independent Review as it was a positive recommendation.

## Outcome:

Recommended.

# Recommended listing

* 1. The sponsor has not provided wording for the proposed grandfathering restriction.
  2. Add new item:

## Initial treatment

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Name, Restriction,  Manner of administration and form | Max.  Qty | №.of  Rpts | Proprietary Name and Manufacturer | |
| Venetoclax  Tablet, 10 mg, 14  Tablet, 50 mg, 7  Tablet, 100 mg, 21 | 1 | 0 | Venclexta® | AbbVie |
| **Category / Program** | GENERAL – General Schedule (Code GE) | | | | |
| **Prescriber type:** | Dental Medical Practitioners Nurse practitioners Optometrists  Midwives | | | | |
| **Episodicity:** | NA | | | | |
| **Severity:** | NA | | | | |
| **Condition:** | Chronic lymphocytic leukaemia | | | | |
| **PBS Indication:** | Chronic lymphocytic leukaemia | | | | |
| **Treatment phase:** | Initial treatment | | | | |
| **Restriction Level / Method:** | Restricted benefit  Authority Required - In Writing  Authority Required - Telephone  Authority Required – Emergency  Authority Required - Electronic  Streamlined | | | | |
| **Treatment criteria:** | NA | | | | |
| **Clinical criteria:** | The treatment must be used as monotherapy,  **AND**  The condition must have relapsed or be refractory to at least one prior therapy,  **AND**  Patient must have a WHO performance status of 0 or 1,  **AND**  Patient must not have previously received PBS-subsidised treatment with this drug,  **AND**  Patient must be considered unsuitable for treatment or retreatment with a purine analogue. | | | | |
| **Population criteria:** | A patient must be considered unsuitable for treatment or retreatment with a purine analogue as demonstrated by at least one of the following:  a) failure to respond (stable disease or disease progression on treatment), or a progression-free interval of less than 3 years from treatment with a purine analogue-based therapy and anti-CD20-containing chemoimmunotherapy regimen after at least two cycles;  b) age is 70 years or older;  c) age is 65 years or older and the presence of comorbidities (Cumulative Illness Rating Scale of 6 or greater, or creatinine clearance of less than 70 mL/min) that might place the patient at an unacceptable risk for treatment-related toxicity with purine analogue-based therapy, provided they have received one or more prior treatment including at least two cycles of an alkylating agent-based (or purine analogue-based) anti-CD20 antibody-containing chemoimmunotherapy regimen;  d) history of purine analogue-associated autoimmune anaemia or autoimmune thrombocytopenia;  e) evidence of one or more 17p chromosomal deletions demonstrated by fluorescence *in situ* hybridisation(FISH). | | | | |
| **Foreword** | NA | | | | |
| **Definitions** | NA | | | | |
| **Prescriber Instructions** | NA | | | | |
| **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. | | | | |
| **Cautions** | NA | | | | |

## Dose holding

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Name, Restriction,  Manner of administration and form | | Max.  Qty | №.of  Rpts | Proprietary Name and Manufacturer | |
| VENETOCLAX  Tablet 10 mg, 14  Tablet 50 mg, 7 | | 1  1 | 0  0 | Venclexta® | AbbVie |
| **Category / Program** | GENERAL – General Schedule (Code GE) | | | | | |
| **Prescriber type:** | Dental Medical Practitioners Nurse practitioners Optometrists  Midwives | | | | | |
| **Episodicity:** | NA | | | | | |
| **Severity:** | NA | | | | | |
| **Condition:** | Chronic lymphocytic leukaemia | | | | | |
| **PBS Indication:** | *C*hronic lymphocytic leukaemia | | | | | |
| **Treatment phase:** | Continuing treatment | | | | | |
| **Restriction Level / Method:** | Restricted benefit  Authority Required - In Writing  Authority Required - Telephone  Authority Required - Emergency  Authority Required - Electronic  Streamlined | | | | | |
| **Treatment criteria:** | NA | | | | | |
| **Clinical criteria:** | The treatment must be used 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. | | | | | |
| **Population criteria:** | NA | | | | | |
| **Foreword** | NA | | | | | |
| **Definitions** | NA | | | | | |
| **Prescriber Instructions** | NA | | | | | |
| **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. | | | | | |
| **Cautions** | NA | | | | | |

## Continuing treatment

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Name, Restriction,  Manner of administration and form | | Max.  Qty | №.of  Rpts | Proprietary Name and Manufacturer | |
| Venetoclax  Tablet, 100 mg, 120 | | 1 | 5 | Venclexta® | AbbVie |
| **Category / Program** | GENERAL – General Schedule (Code GE) | | | | | |
| **Prescriber type:** | Dental Medical Practitioners Nurse practitioners Optometrists  Midwives | | | | | |
| **Episodicity:** | NA | | | | | |
| **Severity:** | NA | | | | | |
| **Condition:** | Chronic lymphocytic leukaemia | | | | | |
| **PBS Indication:** | *C*hronic lymphocytic leukaemia | | | | | |
| **Treatment phase** | Continuing treatment | | | | | |
| **Restriction Level / Method:** | Restricted benefit  Authority Required - In Writing  Authority Required - Telephone  Authority Required – Emergency  Authority Required - Electronic  Streamlined | | | | | |
| **Treatment criteria** | NA | | | | | |
| **Clinical criteria:** | Patient must have previously received PBS-subsidised treatment with this drug for this condition,  **AND**  The treatment must be as monotherapy for seven days, then in combination with rituximab for up to a maximum of six cycles unless rituximab is contraindicated, followed by monotherapy,  **AND**  Patient must not develop progressive disease whilst receiving PBS-subsidised treatment with this drug for this condition,  **AND**  Patient must not receive more than 24 months and seven days of treatment under this restriction. | | | | | |
| **Population criteria:** | NA | | | | | |
| **Foreword** | NA | | | | | |
| **Definitions** | NA | | | | | |
| **Prescriber Instructions** | NA | | | | | |
| **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. | | | | | |
| **Cautions** | NA | | | | | |

# 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.

# Sponsor’s Comment

AbbVie welcomes the decision of the PBAC and is working with the Department of Health on the earliest possible PBS listing.

1. Jones JA, Mato AR, Wierda WG, Davids MS, Choi M, Cheson BD, Furman RR, Lamanna N, Barr PM, Zhou L, Chyla B, Hamed Salem A, Humerickhouse RA, Potluri J, Coutre S, Wayach J & Byrd JC; “Venetoclax for chronic lymphocytic leukaemia progressing after ibrutinib: an interim analysis of a multicentre, open-label, phase 2 trial”; *The Lancet Oncology* (2018); 19(1): 65–75. [↑](#footnote-ref-1)