

## 6.14 VENETOCLAX, Tablet 100 mg, Venclexta<sup>®</sup>, AbbVie Pty Ltd.

### 1 Purpose of submission

- 1.1 The submission requested an Authority Required (Telephone/Online) listing for venetoclax for the treatment of patients with newly diagnosed acute myeloid leukaemia (AML), ineligible for standard intensive remission induction chemotherapy, given in combination with azacitidine. Venetoclax has not previously been considered by the PBAC for this indication.
- 1.2 Listing was requested on the basis of a cost-effectiveness analysis versus azacitidine or low-dose cytarabine (LoDAC) monotherapies.

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

Component	Description
Population	Patients with newly diagnosed acute myeloid leukaemia ineligible for standard intensive induction chemotherapy.
Intervention	Venetoclax 400 mg tablet orally once daily on Days 1-28 each 28 day cycle, following dose ramp-up on Days 1-3 of Cycle 1 (i.e. 100 mg, 200 mg, 400 mg); plus azacitidine 75 mg/m <sup>2</sup> by subcutaneous or intravenous injection once daily on Days 1-7 each 28 day cycle; until disease progression or unacceptable toxicity.
Comparator	Primary: Azacitidine 75 mg/m <sup>2</sup> by subcutaneous or intravenous injection once daily on Days 1-7 each 28 day cycle; until disease progression or unacceptable toxicity. Secondary: Low-dose cytarabine 20 mg by subcutaneous injection twice daily on Days 1-10 each 28 day cycle; until disease progression or unacceptable toxicity.
Outcomes	Overall survival, complete remission, transfusion independence, event free survival, minimal residual disease, and safety.
Clinical claim	Venetoclax with azacitidine is associated with superior efficacy and inferior safety compared to azacitidine monotherapy. Venetoclax with azacitidine is associated with superior efficacy and inferior safety compared to low-dose cytarabine monotherapy.

Source: Table 1-1, p.3 of the submission.

### 2 Background

#### **Registration status**

- 2.1 **TGA status at time of PBAC consideration:** Venetoclax was granted provisional approval by the TGA for the treatment of newly diagnosed AML in adults who are ineligible for intensive chemotherapy as part of combination therapy with LoDAC (28 January 2020) and with azacitidine (5 February 2020).
- 2.2 At the time of PBAC consideration, the regulatory submission to transition the provisional registration to full approval was under evaluation, under a collaborative review initiative with the US Food and Drug Administration (FDA). The US FDA multi-

discipline review was available (in lieu of a TGA-branded Clinical Evaluation Report). The FDA approved venetoclax for the treatment of AML in combination with azacitidine or low-dose cytarabine or decitabine (16 October 2020).

- 2.3 The requested final indication for venetoclax was consistent with the provisionally approved indication.
- 2.4 Azacitidine has an ARTG listing for patients with myelodysplastic syndromes (MDS), chronic myelomonocytic leukaemia (CMML), and AML with 20-30% blasts and multi-lineage dysplasia.

*For more detail on the PBAC’s view, see section 7 PBAC outcome.*

### 3 Requested listing

- 3.1 Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with strikethrough.

Name, restriction, manner of administration, form	Maximum quantity (packs)	Maximum amount (units)	No. of repeats	Dispensed price for maximum quantity	Proprietary name and manufacturer
VENETOCLAX 100 mg tablet, 120	1	120	5 0	\$7,799.98 (published) \$ [REDACTED] (effective)	VENCLEXTA®, AbbVie Pty Ltd
<b>Category / Program:</b> GENERAL – General Schedule (Code GE)					
<b>Prescriber type:</b> <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives					
<b>Restriction Type – assessment time by Services Australia – Method of obtaining authority approval (if Authority Required)</b>					
<input checked="" type="checkbox"/> Authority Required – immediate/real time assessment by Services Australia (telephone/electronic)					
<b>Episodicity:</b> <del>Untreated/newly diagnosed</del>					
<b>Condition:</b> Acute myeloid leukaemia (AML)					
<b>Indication:</b> <del>Newly diagnosed</del> acute myeloid leukaemia (AML)					
<b>Treatment Phase:</b> Initial treatment					
<b>Clinical criteria:</b>					
<del>Patient must not have previously received PBS-subsidised treatment with this drug for this condition</del>					
AND					
<del>Patient must not have received a prior line of treatment for this condition</del>					
<i>The condition must be previously untreated at the time of initiation with this drug</i>					
AND					
Patient must not be considered eligible for standard intensive remission induction chemotherapy					
AND					
<i>The treatment must be used in combination with azacitidine for this condition (refer to Product Information for timing of azacitidine and venetoclax doses)</i>					
AND					
<i>Patient must not have developed disease progression while receiving PBS-subsidised treatment with this drug for this condition</i>					
AND					
<i>Patient must not have acute promyelocytic leukaemia</i>					
<b>Prescribing Instructions:</b>					
Progressive disease monitoring via a complete blood count must be taken at the end of each cycle.					

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<p>If abnormal blood counts suggest the potential for relapsed AML, a bone marrow biopsy must be performed to confirm the absence of progressive disease for the patient to be eligible for further cycles.  A patient who has progressive disease when treated with this drug is no longer eligible for PBS-subsidised treatment with this drug.  Patients will still be considered eligible despite receiving prior, but essential treatment with hydroxyurea or leukapheresis  <del>Patients with acute promyelocytic leukaemia are not eligible for treatment.</del></p> <p><b>Administrative Advice:</b>  No increase in the maximum number of repeats may be authorised.  No increase in the maximum quantity or number of units may be authorised.  Special Pricing Arrangements apply.  Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see <a href="http://www.servicesaustralia.gov.au/HPOS">www.servicesaustralia.gov.au/HPOS</a>) or by telephone by contacting Services Australia on 1800 888 333.</p>
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<b>Category / Program:</b> GENERAL – General Schedule (Code GE)
<b>Prescriber type:</b> <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>Restriction Type / Method:</b> <input checked="" type="checkbox"/> Authority Required – immediate/real time assessment by Services Australia (telephone/online application avenues)
<b>Condition:</b> Acute myeloid leukaemia (AML)
<b>Indication:</b> Acute myeloid leukaemia (AML)
<b>Treatment Phase:</b> Continuing treatment
<b>Clinical criteria:</b>
Patient must have previously received PBS-subsidised treatment with this drug for this condition
AND
Patient must not have developed disease progression while receiving PBS-subsidised treatment with this drug for this condition
AND
The treatment must be in combination with azacitidine for this condition
<b>Prescribing Instructions:</b>
Progressive disease monitoring via a complete blood count must be taken at the end of each cycle. If abnormal blood counts suggest the potential for relapsed AML, a bone marrow biopsy must be performed to confirm the absence of progressive disease for the patient to be eligible for further cycles. A patient who has progressive disease when treated with this drug is no longer eligible for PBS-subsidised treatment with this drug

- 3.2 The submission requested a special pricing arrangement with a published price of \$7,799.98 (DPMQ) and an effective price of \$ [REDACTED] (DPMQ). [REDACTED]. However, new fees were introduced on 1 January 2021, and the DPMQ is now \$7,784.18.
- 3.3 The submission anticipated that venetoclax would be administered in the hospital setting, either as inpatient or at the day-stay unit, during the ramp-up phase (days 1-4) to monitor for TLS. When venetoclax is co-administered with strong or moderate CYP3A inhibitors, dose reductions are recommended to reduce the risk of TLS. However, the submission did not request listings for the venetoclax 10 mg and 50 mg

dose strengths, stating that the sponsor will work with hospitals to provide access in this situation.

- 3.4 The requested restriction is narrower than the venetoclax provisional TGA indication, as eligible patients must be treated with venetoclax in combination therapy with azacitidine (excludes combination therapy with LoDAC or other agents).
- 3.5 The ESC noted that clinical criteria for ‘ineligibility’ for standard intensive remission induction chemotherapy and disease progression are not defined and will most likely be determined on a patient-by-patient basis by treating physicians. The evaluation considered that the listing of venetoclax in combination with azacitidine on the PBS as an effective treatment for AML in patients unfit for (i.e. unsuitable, or unable to tolerate) standard intensive remission induction chemotherapy, may impact physician and patient choice of treatment options, and provide an alternative to standard intensive remission induction chemotherapy for some patients. The Pre-Sub-Committee Response (PSCR) argued that if patients are deemed eligible for a potentially curative induction chemotherapy regimen, it is unlikely that this would be forgone for low-intensity non-curative options. The ESC agreed, but also advised that a small risk of leakage remained for patients whose eligibility for a curative regimen was “borderline”.
- 3.6 Azacitidine is currently listed on the PBS for use in AML with 20-30% bone marrow blasts and multi-lineage dysplasia, for MDS, or for CMML. The submission requested that the current PBS listing for azacitidine be amended to allow use in AML patients regardless of blast cell count and presence of multi-lineage dysplasia when used in combination with venetoclax. The ESC noted that at the time of PBAC consideration (2009), the WHO classification scheme for MDS included refractory anaemia (with or without excess blasts), CMML without myeloproliferative disease, and AML with blasts of between 20-30%. As such, the intent of the PBS listing was for treatment of patients with MDS, not AML per se.
- 3.7 The submission requested grandfathering provisions for patients receiving non-PBS subsidised venetoclax prior to PBS listing. The PBAC noted that no further details were provided.

*For more detail on the PBAC’s view, see section 7 PBAC outcome.*

## **4 Population and disease**

- 4.1 AML is the most common acute leukaemia in adults, with an estimated incidence in the Australian setting of 3.8 per 100,000 (age standardised incidence) or 4.3 per 100,000 (average age specific incidence; AIHW Cancer data in Australia, 2020). The onset and progression of AML is typically rapid with presentation and diagnosis occurring within weeks of the onset of symptoms (Estey & Döhner, 2006). Median age at diagnosis is 70.4 years in males (56.4% of cases) and 65.6 years in females (43.6% of cases). The five-year relative survival of AML is 27.7% (AIHW, 2020), with both incidence and mortality increasing with age.

- 4.2 Presentation is typically either de novo (AML not related to prior disease), or secondary (AML related to prior MDS, myeloproliferative disorder, or aplastic anaemia, that converts to myeloid leukaemia). Prognosis and response to therapies varies by age and cytogenetic risk.
- 4.3 AML is defined as the presence of  $\geq 20\%$  blasts in the bone marrow or peripheral blood. Diagnosis is confirmed on morphologic assessment of bone marrow specimens and blood smears, patient and family history, analysis of the expression of cell-surface or cytoplasmic markers by means of flow cytometry, identification of chromosomal findings by means of conventional cytogenetic testing and screening for selected molecular genetic lesions (Döhner et al., 2015a; Heuser et al., 2020). Diagnosis may also be confirmed in patients with less than 20% blasts by recurrent cytogenetic abnormalities including t(15;17), t(8;21), t(16;16), or inv(16) or the corresponding transcript (National Comprehensive Cancer Network, NCCN, 2020).
- 4.4 A diagnosis with AML may be preceded by MDS, a group of haematologic malignancies characterised by clonal haematopoiesis and abnormal cellular maturation, clinically similar to AML but with a lower percentage of blasts in the bone marrow peripheral blood (<20% blasts). Patients with MDS may experience anaemia, infection and/or bleeding, and disease progression or transformation to AML. Treatment for MDS may include watchful waiting, supportive therapies or in high-risk cytogenetic subgroups or variants (e.g. CMML), standard or low intensity chemotherapy (e.g. azacitidine). Patients who have progressed to AML from MDS after significant exposure to hypomethylating agents (HMA) may be less likely to benefit from continued treatment with a HMA compared to treatment naïve patients.
- 4.5 Standard intensive induction chemotherapy for treatment naïve AML is commonly cytarabine combined with an anthracycline (i.e. '7+3' regimen) with or without cytogenetic targeted therapies, followed by high intensity consolidation therapy; e.g. intermediate or high dose cytarabine or allogeneic haematopoietic stem cell transplantation (NCCN, 2020), and has been associated with increased mortality and morbidity, and prolonged hospitalisation in unfit patients. Patients unfit for intensive induction chemotherapy are treated with HMAs (e.g. azacitidine), LoDAC, other low intensity therapies, or best supportive care.
- 4.6 The proposed clinical management algorithm places venetoclax with azacitidine as an alternative to low intensity azacitidine or LoDAC, for patients with previously untreated AML, unfit for intensive induction chemotherapy.

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

## **5 Comparator**

- 5.1 The submission nominated azacitidine monotherapy as the main comparator, and LoDAC as a secondary comparator (with a 55.6%/44.4% split in the economic evaluation; and 50%/50% market share in the financial estimates). The submission argued that this is consistent with the use of low intensity therapies recommended in

international clinical guidelines for treatment naïve AML in patients unsuitable for intensive induction chemotherapy. Azacitidine and LoDAC are recommended for use as low intensity therapies in the requested population. However, excepting specific cytogenetic risks, there was no overall preference for azacitidine over cytarabine in the clinical guidelines.

- 5.2 As noted above, azacitidine is not listed on the ARTG or PBS for use in the requested indication, and existing azacitidine PBS listings would require amendment to facilitate use of venetoclax in combination with azacitidine in the requested population. Azacitidine is currently PBS-listed as a section 100 Highly Specialised Drug, for use in AML with 20-30% bone marrow blasts and multi-lineage dysplasia. The ESC noted that at the time of PBAC recommendation (2009), this group of patients were classified as having MDS. The submission stated that access to azacitidine in patients with >30% blasts is supported by some major hospitals, and that a sponsor of azacitidine offers a capped expenditure program for the use of azacitidine where it is not subsidised. While there may be some overlap between the current azacitidine PBS listing and the requested population, the extent of overlap is most likely small.
- 5.3 Cytarabine has an unrestricted listing on the ARTG and PBS Efficient Funding of Chemotherapy Schedule, and is subsidised for use in the requested population. Consequently, LoDAC may be the comparator most likely to be replaced in clinical practice. The PSCR argued that the results of the CURRENT study, an Australian real-world observational study of treatment patterns and clinical outcomes in unfit AML patients, which was provided with the submission, indicate that the majority of new diagnosed AML patients treated with low-intensity therapy undergo treatment with azacitidine. It further argued that this was consistent with local clinician advice, supporting azacitidine as the most likely therapy to be replaced on the PBS. It suggested that LoDAC was the comparator for patients who are ineligible, contraindicated or do not have access to azacitidine. The ESC noted that Attachment 1 of the submission contained tables and figures from the CURRENT study, but no information was available on authorship or patient selection, and the trial was not included in the Australian New Zealand Clinical Trial Registry. Furthermore, it did not provide information of first-line systemic therapy by subgroups based on blast cell counts (i.e. < 20%, 20-30%, > 30%). As such, it was unreliable and uninformative for establishing the relative weighting of azacitidine as part of the comparator mix for this submission.
- 5.4 The ESC advised that a mixed comparator was appropriate, but noting the above paragraphs, this should be heavily weighted towards LoDAC.

*For more detail on the 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 discussed the natural history of the disease, current and historical treatment approaches, and how the drug would be used in practice. The clinician highlighted that azacitidine is the current treatment of choice for this patient population in other jurisdictions, and although it is not currently available on the PBS, there is a strong desire for its wider availability as there are few agents available in this population. The clinician discussed the results of the VIALE-A study (M15-656), a head-to-head randomised trial comparing venetoclax with azacitidine versus azacitidine, highlighting similarities between the control arm and patients in the Australasian Leukaemia and Lymphoma Group National Blood Cancer Registry (ALLG NBCR) receiving low-intensity therapy. The clinician stated that the venetoclax arm in VIALE-A had seen earlier and more durable response results, with lower risk of infection and less dependence on blood transfusions, all contributing to an improved overall survival. In terms of how venetoclax may be used in practice, the clinician highlighted that ultimately the decision to initiate low-intensity chemotherapy was at the discretion of clinicians and according to patient preferences.

### ***Consumer comments***

6.2 The PBAC noted and welcomed the input from the Leukaemia Foundation and Rare Cancers Australia, via the Consumer Comments facility on the PBS website. The comments described individual patient experiences of the benefits of treatment with venetoclax including the convenience and tolerability of an oral therapy, and returning to a normal work and family life after commencing treatment.

### ***Clinical trials***

6.3 The submission presented comparisons between venetoclax with azacitidine versus each of the two nominated comparators, azacitidine low intensity therapy and LoDAC:

- A direct comparison of venetoclax with azacitidine versus azacitidine, based on one head-to-head randomised trial (M15-656);
- An indirect treatment comparison of venetoclax with azacitidine (M15-656) versus LoDAC (AZA-AML-001) with azacitidine as a common reference;
- An indirect treatment comparison of venetoclax with azacitidine (M15-656) versus LoDAC (meta-analysis of AZA-AML-001 and AZA-001) with azacitidine as a common reference as a sensitivity analysis; and
- A propensity score weighted analysis of venetoclax with azacitidine (M15-656) versus LoDAC (M16-043) as a supporting analysis.

6.4 The submission also presented a direct comparison of venetoclax with LoDAC versus LoDAC (M16-043) as a supporting analysis. It was acknowledged that a listing for

venetoclax with LoDAC was not requested in the current submission, and the comparison was provided as selected results were used to inform the economic model.

6.5 The PBAC previously reviewed the AZA-001 trial in the July 2009 consideration of azacitidine for the treatment of myelodysplastic syndromes, chronic myelomonocytic leukaemia, and AML.

6.6 Details of the trials presented in the submission are provided in the table below.

**Table 2: Trials and studies presented in the submission**

Trial ID	Protocol title/ Publication title	Publication citation
M15-656	A randomized, double-blind, placebo controlled phase 3 study of venetoclax in combination with azacitidine versus azacitidine in treatment naïve subjects with acute myeloid leukemia who are ineligible for standard induction therapy. (NCT02993523)	Interim Clinical Study Report: 8 May 2020.
	DiNardo, C. D., Jonas, B. A., Pullarkat, V., et al. Azacitidine and venetoclax in previously untreated acute myeloid leukaemia.	<i>New England Journal of Medicine</i> 2020, 383(7):617-629.
	Potturi, J., Xu, T., Hong, W. J., et al. Phase 3, randomised, double-blind, placebo-controlled study of venetoclax combined with azacitidine versus azacitidine in treatment-naïve patients with acute myeloid leukaemia.	<i>Journal of Clinical Oncology</i> 2017, 35(15): Abstract TPS7069.
M16-043	A randomized, double-blind, placebo controlled phase 3 study of venetoclax co-administered with low dose cytarabine versus low dose cytarabine in treatment-naïve patients with acute myeloid leukemia who are ineligible for intensive chemotherapy.	Clinical Study Report: 20 March 2020.
	Wei, A. H., Montesinos, P., Ivanov, V., et al. Venetoclax plus LDAC for newly diagnosed AML ineligible for intensive chemotherapy: a phase 3 randomised placebo-controlled trial.	<i>Blood</i> 2020, 135(24):2137-2145.
	Wei, A. H., Montesinos, P., Ivanov, V., et al. A phase 3 study of venetoclax plus low dose cytarabine in previously untreated older patients with acute myeloid leukaemia (viale-C): A 6-month update.	<i>HemaSphere</i> 2020, 4: Abstract 19-20.
AZA-AML-001	Dombret, H., et al. International phase 3 study of azacitidine vs conventional care regimens in older patients with newly diagnosed AML with >30% blasts.	<i>Blood</i> 2015, 126(3):291-299.
	Seymour, J. F., et al. Azacitidine improves clinical outcomes in older patients with acute myeloid leukaemia with myelodysplasia-related changes compared with conventional care regimens.	<i>BMC Cancer</i> 2017, 17(1):852.
	Seymour, J. F., et al. Incidence rates of treatment emergent adverse events and related hospitalisation are reduced with azacitidine compared with conventional care regimens in older patients with acute myeloid leukaemia.	<i>Leukaemia and Lymphoma</i> 2017, 58(6):1412-1423.
AZA-001	Fenaux, P., et al. Azacitidine prolongs overall survival compared with conventional care regimens in elderly patients with low bone marrow blast count acute myeloid leukaemia.	<i>Journal of Clinical Oncology</i> 2010, 28(4):562-569.
	Fenaux, P., et al. Prolonged survival with improved tolerability in higher risk myelodysplastic syndromes: Azacitidine compared with low dose ara-C.	<i>British Journal of Haematology</i> 2010, 149(2):244-249.
	Seymour, J. F., et al. Effects of azacitidine compared with conventional care regimens in elderly (≥75 years) patients with higher risk myelodysplastic syndromes.	<i>Critical Reviews in Oncology / Haematology</i> 2010, 76(3):218-227.

Source: Table 2-6, pp.48-51 of the submission.

6.7 The key features of the trials included in the submission are summarised in the table below.

Table 3: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in model
<b>Venetoclax 400 mg + azacitidine versus placebo + azacitidine</b>						
M15-656	433	Phase III, R, DB, PC, MC Treatment to disease progression or discontinuation (follow-up ongoing).	Low	Adults ≥ 18 years, Treatment naïve AML, not eligible for standard induction therapy due to age or comorbidities.	Primary: OS, CR + CRi Secondary: EFS, CR, CRi, CRh, TIR, MRD, QoL, Safety.	OS, EFS, CR/CRi, TTD for VTX+AZA and AZA arms
<b>Venetoclax 600 mg + LoDAC versus placebo + LoDAC</b>						
M16-043	221	Phase III, R, DB, PC, MC Treatment to disease progression or discontinuation (follow-up ongoing)	Low	Adults ≥ 18 years, Treatment naïve AML, not eligible for standard induction therapy due to age or comorbidities.	Primary: OS Secondary: OS at 1 year, EFS, CR, CRi, PR, TIR, QoL, Safety.	EFS, CR/CRi, TTD for LoDAC arm
<b>Azacitidine versus LoDAC</b>						
AZA-AML-001	488	Phase III, R, OL, MC Treatment to disease progression or discontinuation	High	Adults ≥ 65 years, Treatment naïve AML, > 30% bone marrow blasts.	Primary: OS Secondary: OS at 1 year, EFS, CR, CRi, PR, TIR, Safety.	OS for LoDAC arm
AZA-001	358	Phase III, R, OL, MC Treatment to disease progression or discontinuation	High	Adults ≥ 18 years, High risk MDS, ≥ 10% bone marrow blasts WBC count < 13 × 10 <sup>9</sup> /L (N=358); of which, 113 patients met WHO AML criteria.	Primary: OS Secondary: Time to transform to AML, TIR, haematological response, Safety.	Not used

Source: Table 2-7, pp.54-56 of the submission.

Abbreviations; AML, acute myeloid leukaemia; AZA, azacitidine; CR, complete remission; CRi, complete remission with incomplete blood count recovery; CRh, complete remission with partial haematologic recovery; DB, double blind; EFS, event free survival; LoDAC, low-dose cytarabine; MC, multi-centre; MRD, minimal residual disease; OL, open label; OS, overall survival; PR, partial response QoL, quality of life; R, randomised; TIR, transfusion independence rate; TTD, time to treatment discontinuation; VTX, venetoclax; WHO, World Health Organization.

6.8 The M15-656 and M16-043 trials were randomised controlled trials with low risk of bias, which enrolled adult patients with treatment naïve AML unfit for intensive induction chemotherapy. Inclusion criteria were very similar between trials and included extensive criteria for the identification of patients unfit for intensive induction chemotherapy based on age ≥75 years, or age 18-74 years with comorbidities likely to impact fitness for intensive induction chemotherapy (assessed by treating physicians), ECOG status, renal function and hepatic function. The most prevalent reason for patients being unfit for intensive induction chemotherapy in both trials was ECOG status 2-3.

6.9 There were differences between the two trials in terms of the proportions of de novo (M15-656 75.2% vs M16-043 61.6%) versus secondary AML (24.8% vs 38.4%), and prior use of HMA medicines (0 vs 19.9%). The ESC noted that prior treatment of MDS was allowed in M16-043, except for cytarabine, and no prior therapy was permitted in M15-656. Both trials were inconsistent with the proposed PBS population since a

proportion of AML patients in Australia have had prior MDS and may have accessed azacitidine or cytarabine treatment (in the CURRENT study, 25.7% of patients had prior HMA therapy). In addition, patients with favourable risk cytogenetics such as t(8;21), inv(16), t(16;16) or t(15;17) were excluded from Trial M15-656, but included in Trial M16-043, however the proportions of patients with favourable risk cytogenetics enrolled in Trial M16-043 were very small. The ESC advised that the trials were skewed towards patients with poorer prognosis AML.

- 6.10 The AZA-AML-001 trial included a broader range of patients aged  $\geq 65$  years with treatment naïve AML and  $>30\%$  bone marrow blasts, stratified by fitness for intensive induction chemotherapy with the subgroup of patients pre-selected for low intensity therapies randomised to azacitidine (N=154) or LoDAC (N=158). Similarly the AZA-001 trial included patients aged  $\geq 18$  years with higher risk myelodysplastic syndrome or chronic myelomonocytic leukaemia, with small subgroups classified as treatment naïve AML randomised to azacitidine (N=14) or LoDAC (N=20).
- 6.11 The risk of bias in the AZA-AML-001 and AZA-001 studies was considered high, given the open label design, initial allocation to intensive induction therapy, low intensity chemotherapy or best supportive care prior to randomisation, and knowledge of the treatment allocation. There were substantial differences between the AZA-AML-001 and AZA-001 trials in terms of age, gender and ECOG status, and the fact that AZA-001 excluded patients with secondary MDS or therapy related disease. The applicability of both trials to the requested population was uncertain (see indirect comparison below).

### ***Comparative effectiveness***

- 6.12 The results of the venetoclax with azacitidine versus azacitidine (direct comparison), and the venetoclax with azacitidine versus LoDAC (indirect treatment comparison and propensity score weighted analysis) are presented below. The venetoclax with LoDAC versus LoDAC direct comparison was presented in the commentary.

### **Venetoclax with azacitidine vs azacitidine (direct comparison)**

- 6.13 Table 4 summarises the results for overall survival for Trial M15-656 in the full analysis set at the data cut-off of 4 January 2020, with the associated Kaplan Meier plot in Figure 1.

**Table 4: Results of overall survival from M15-656 (FAS Group 2; 4 Jan 2020 cut-off; median duration of follow up 20.4 months)**

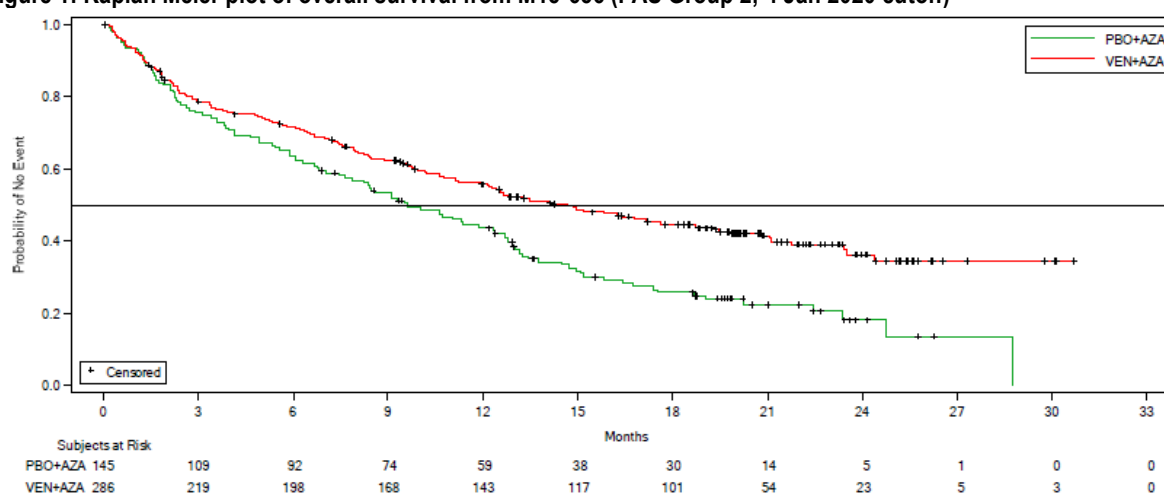
	<b>VTX + AZA (N=286)</b>	<b>Pbo + AZA (N=145)</b>
<b>Overall survival</b>		
Patients with event (death), n (%)	161 (56.3%)	109 (75.2%)
Median time to event, months (95% CI)	14.7 (11.9, 18.7)	9.6 (7.4, 12.7)
Stratified HR (95% CI) <sup>a</sup>	<b>0.662 (0.518, 0.845)</b>	
Overall survival at 6 month, % (95% CI)	71.9 (66.3, 76.8)	63.9 (55.5, 71.2)
Overall survival at 12 month, % (95% CI)	55.8 (49.7, 61.5)	43.8 (35.5, 51.8)
Overall survival at 24 month, % (95% CI)	36.5 (29.7, 43.4)	18.3 (11.1, 27.0)

Source: Table 2-31, p.123 of the submission. Statistically significant results in bold.

Abbreviations: AZA, azacitidine; CI, confidence interval; FAS, full analysis set; HR, hazard ratio; Pbo, placebo; OS, overall survival; VTX, venetoclax.

<sup>a</sup> Stratified by age (18 - < 75, ≥ 75) and cryptogenic risk (intermediate, poor).

**Figure 1: Kaplan Meier plot of overall survival from M15-656 (FAS Group 2; 4 Jan 2020 cutoff)**



Source: Figure 2-12, p.124 of the submission.

Abbreviations: AZA, azacitidine; CI, confidence interval; FAS, full analysis set; HR, hazard ratio; PBO, placebo; VEN, venetoclax.

Note: Stratified by age (18 - < 75, ≥ 75) and cryptogenic risk (intermediate, poor). Censored at last known alive date prior to cut-off.

- 6.14 Patients treated with venetoclax with azacitidine experienced a statistically significant improvement in overall survival compared to patients treated with azacitidine (HR 0.66, 95% CI: 0.52, 0.85), with an increase in median overall survival of 5.1 months over a median follow up of 20.4 months.
- 6.15 Table 5 summarises the results for investigator and IRC assessed event free survival for Trial M15-656 in the full analysis set at the data cut-off of 4 January 2020, with the associated Kaplan Meier plot for investigator assessed event free survival in Figure 2.

**Table 5: Event free survival from M15-656 (FAS Group 2; 4 Jan 2020 cut-off)**

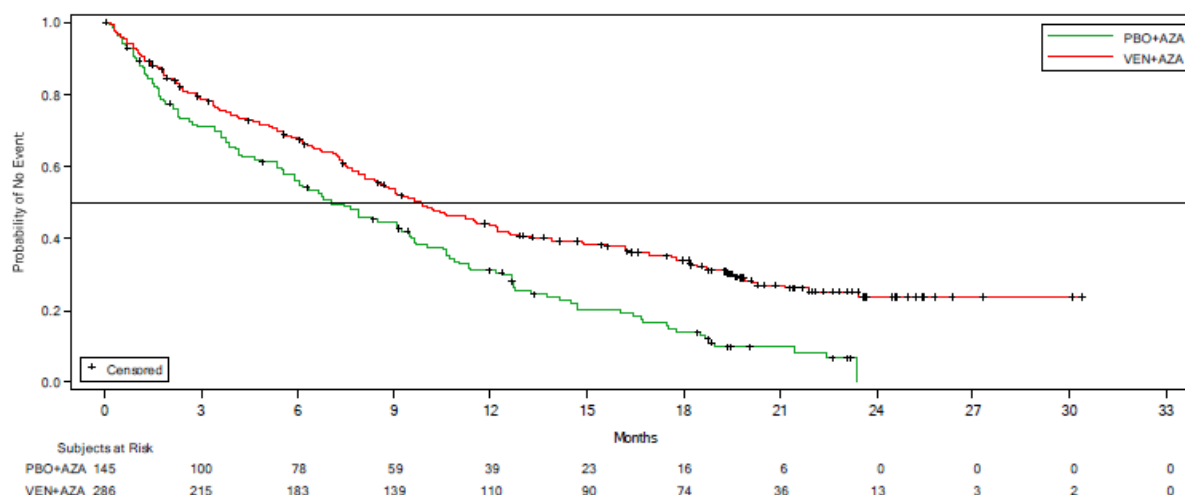
	Investigator assessed		IRC assessed	
	VTX + AZA (N=286)	Pbo + AZA (N=145)	VTX + AZA (N=286)	Pbo + AZA (N=145)
<b>Event free survival</b>				
Patients with event, n (%)	191 (66.8%)	122 (84.1%)	190 (66.4%)	120 (82.8%)
Confirmed MR/PD, n/N (%)	83/191 (43.5%)	35/122 (28.7%)	79/190 (41.6%)	30/120 (25.0%)
Treatment failure, n/N (%)	4/191 (2.1%)	12/122 (9.8%)	3/190 (1.6%)	11/120 (9.2%)
Death (any cause), n/N (%)	104/191 (54.5%)	75/122 (61.5%)	108/190 (56.8%)	79/120 (65.8%)
Median time to event, months (95% CI)	9.8 (8.4, 11.8)	7.0 (5.6, 9.5)	9.8 (8.5, 12.0)	7.9 (5.9, 9.5)
Stratified HR (95% CI) <sup>a</sup>	<b>0.632 (0.502, 0.796)</b>		<b>0.643 (0.510, 0.811)</b>	
EFS at 6 months, % (95% CI)	67.7 (61.8, 72.8)	56.2 (47.6, 63.9)	68.8 (63.0, 73.9)	58.1 (49.5, 65.8)
EFS at 12 months, % (95% CI)	43.5 (37.4, 49.3)	31.3 (23.6, 39.2)	44.1 (38.0, 49.9)	32.2 (24.5, 40.2)
EFS at 24 months, % (95% CI)	23.8 (17.9, 30.2)	NA	23.8 (17.9, 30.2)	NA

Source: Tables 2-39 and 2-40 of the submission. Statistically significant results in bold.

Abbreviations: AZA, azacitidine; CI, confidence interval; EFS, event free survival; FAS, full analysis set; HR, hazard ratio; IRC, independent review committee; MR, morphological relapse; NA, not available; PBO, placebo; PD, progressive disease; VTX, venetoclax

<sup>a</sup>Stratified by age (18 - < 75, ≥ 75) and cytogenetics (intermediate risk, poor risk) from Interactive Voice Response System (IVRS)/Interactive Web Response System (IWRS).

**Figure 2: Kaplan Meier EFS by investigator assessment from M15-656 (FAS Group 2; 4 Jan 2020 cutoff)**



Source: Figure 2-15, p.134 of the submission.

Abbreviations: AZA, azacitidine; CI, confidence interval; EFS, event free survival; FAS, full analysis set; HR, hazard ratio; PBO, placebo; VEN, venetoclax.

Note: Stratified by AML status (de novo, secondary), and age (18 - < 75, ≥ 75). Participants without events (i.e. morphological relapse, disease progression, treatment failure, or death) censored at date last known to be event free.

- 6.16 Patients treated with venetoclax with azacitidine experienced a statistically significant improvement in investigator assessed event free survival compared to patients treated with azacitidine (HR 0.63, 95% CI: 0.50, 0.80), with an increase in median event-free survival of 2.8 months over a median follow up of 20.4 months. Results for IRC assessed event free survival also statistically significantly favoured venetoclax with azacitidine (HR 0.64, 95% CI: 0.51, 0.81).
- 6.17 The distribution of events contributing to event free survival differed between treatment arms. A lower proportions of patients experiencing death (VTX+AZA 54.5%

vs AZA 61.5%) or treatment failure (VTX+AZA 2.1% vs AZA 9.8%), but a higher proportion of morphological relapse or disease progression (VTX+AZA 43.5% vs AZA 28.7%) in the venetoclax with azacitidine arm compared to the azacitidine arm in investigator assessed results.

- 6.18 Table 6 summarises the results for investigator and IRC assessed best response, for complete remission, and the composite outcome of complete remission and complete remission with incomplete blood count recovery.

**Table 6: Best response of CR and CR + CRi from M15-656 (FAS Group 2; 4 Jan 2020 cut-off)**

	Investigator assessed		IRC assessed	
	VTX + AZA (N=286)	Pbo + AZA (N=145)	VTX + AZA (N=286)	Pbo + AZA (N=145)
<b>Best response of CR + CRi (IWG criteria)</b>				
CR + CRi rate, n (%)	190 (66.4%)	41 (28.3%)	178 (62.2%)	39 (26.9%)
Odds ratio (95% CI) <sup>a</sup>	<b>5.02 (3.24, 7.77)<sup>a</sup></b>		<b>4.48 (2.89, 6.94)<sup>a</sup></b>	
CR rate, n (%)	105 (36.7%)	26 (17.9%)	72 (25.2%)	25 (17.2%)
Odds ratio (95% CI) <sup>a</sup>	<b>2.66 (1.63, 4.32)<sup>a</sup></b>		1.61 (0.97, 2.68) <sup>a</sup>	
CRi rate, n (%)	85 (29.7%)	15 (10.3%)	106 (37.1%)	14 (9.7%)
<b>Other response outcomes (IWG criteria)</b>				
Partial remission, n (%)	3 (1.0%)	3 (2.1%)	3 (1.0%)	5 (3.4%)
MLFS, n (%)	24 (8.4%)	6 (4.1%)	29 (10.1%)	5 (3.4%)
Resistant disease, n (%)	36 (12.6%)	69 (47.6%)	40 (14.0%)	70 (48.3%)
Progressed disease, n (%)	3 (1.0%)	6 (4.1%)	2 (0.7%)	5 (3.4%)
Discontinued, no data, n (%)	30 (10.5%)	20 (13.8%)	34 (11.9%)	21 (14.5%)

Source: Tables 2-33 and 2-34, pp.126-127 of the submission.

Abbreviations: AZA, azacitidine; CI, confidence interval; CR, complete remission; CRi, complete remission with incomplete blood count recovery; FAS, full analysis set; IRC, independent review committee; IWG, International Working Group; MLFS, morphologically leukaemia free state; PBO, placebo; VTX, venetoclax.

<sup>a</sup> Calculated for the submission post-hoc using Review Manager 5.4 (Attachment 5 of the submission).

Note: Patients randomised but with no disease assessment were treated as non-responders.

- 6.19 Statistically significantly larger proportions of patients treated with venetoclax with azacitidine assessed by investigators, achieved complete remission (CR; odds ratio 2.66, 95% CI: 1.63, 4.32), and the composite of complete remission or complete remission with incomplete blood count recovery (CR + CRi; odds ratio 5.02, 95% CI: 3.24, 7.77) compared to azacitidine alone. Similar results were reported for the IRC assessed composite of CR + CRi. However, results of the IRC assessed CR favoured venetoclax + azacitidine, but were not statistically significant. Other outcomes of response to treatment consistently favoured venetoclax with azacitidine.
- 6.20 Statistically significantly larger proportions of patients treated with venetoclax with azacitidine achieved red blood cell (RBC) and/or platelet transfusion independence, experiencing 56 days without a RBC and/or platelet transfusion, compared to azacitidine alone (odds ratio 2.71, 95% CI: 1.79, 4.11).
- 6.21 Baseline EQ-5D index scores were similar for patients treated with venetoclax with azacitidine (0.76) compared to azacitidine alone (0.70), remained similar at each reference point up to Cycle 21, and showed no statistically significant difference between treatment arms in change from baseline at any reference point.

- 6.22 Similarly, there was no statistically significant difference between treatment arms in change from baseline in EORTC QLQ-C30 scores between patients treated with venetoclax with azacitidine compared to azacitidine alone at any reference point.

**Venetoclax with azacitidine vs LoDAC (indirect treatment comparison, ITC)**

- 6.23 The Bucher method was used for the analysis of the indirect treatment comparison of venetoclax with azacitidine compared to LoDAC, based on the results for overall survival (hazard ratios) and remission rates (odds ratio) from the M15-656 and AZA-AML-001 trials. The transitivity and comparability between trials was not adequately addressed in the submission.
- 6.24 There were substantial differences between the AZA-AML-001 and AZA-001 trials in terms of age, gender and ECOG status. The AZA-AML-001 study included subjects aged  $\geq 65$  years with newly diagnosed de novo or secondary AML, while the AZA-001 trial included patients aged  $\geq 18$  years with myelodysplastic syndrome or chronic myelomonocytic leukaemia, and excluded patients with secondary or treatment related AML. Meta-analysis of the AZA-AML-001 and AZA-001 trials may not be appropriate. The applicability of the AZA-AML-001 and AZA-001 low intensity therapy subgroups was not adequately explained and may not be reasonable.
- 6.25 There were substantial differences between the M15-656 trial and the AZA-AML-001 and AZA-001 studies in terms of inclusion criteria, history of prior myelodysplastic syndrome and baseline ECOG status. Insufficient data were provided for the criteria used to select patients for low intensity therapies, as well as patient demographic and baseline disease characteristics of the AZA-AML-001 and AZA-001 low intensity azacitidine subgroups, and therefore, appropriate evaluation of the studies and the ITC was limited.
- 6.26 Table 7 summarises the results for overall survival in the indirect treatment comparison between venetoclax with azacitidine versus LoDAC, and sensitivity analysis including a meta-analysis of the AZA-AML-001 and AZA-001 studies.

**Table 7: Results of overall survival in the indirect comparison of venetoclax + azacitidine versus LoDAC**

Trial	Median time to event, months (95% CI)			Hazard ratio (95% CI)
	VTX + AZA	AZA	LoDAC	
M15-656	N=286 14.7 (11.9, 18.7)	N=145 9.6 (7.4, 12.7)	-	<b>0.66 (0.52, 0.85)</b>
AZA-AML-001	-	N=154 11.2 (8.8, 13.4)	N=158 6.4 (4.8, 9.1)	0.90 (0.70, 1.16)
<b>Indirect treatment comparison VTX + AZA versus LoDAC; HR (95% CI)</b>				<b>0.596 (0.419, 0.847)</b>
<b>Sensitivity analysis (meta-analysis of AZA-AML-001 and AZA-001)</b>				
M15-656	N=286 14.7 (11.9, 18.7)	N=145 9.6 (7.4, 12.7)	-	<b>0.66 (0.52, 0.85)</b>
AZA-AML-001	-	N=154 11.2 (8.8, 13.4)	N=158 6.4 (4.8, 9.1)	0.90 (0.70, 1.16)
AZA-001	-	N=14 24.5 (18.4, NR)	N=18 17.0 (14.5, 25.8)	0.37 (0.12, 1.14)
Pooled treatment comparison LoDAC; HR (95% CI)				0.69 (0.31, 1.53)
<b>Indirect treatment comparison VTX + AZA versus LoDAC; HR (95% CI)</b>				<b>0.457 (0.198, 1.053)</b>

Source: Tables 2-72 and 2-73, p.188 of the submission. Statistically significant results in bold.

Abbreviations: AZA, azacitidine; CI, confidence interval; HR, hazard ratio; LoDAC, low-dose cytarabine; VTX, venetoclax.

- 6.27 Patients treated with venetoclax with azacitidine experienced a statistically significant improvement in overall survival compared to patients treated with LoDAC (HR 0.60, 95% CI: 0.42, 0.85). Sensitivity analysis using a meta-analysis of the AZA-AML-001 and AZA-001 studies in the indirect analysis provided a hazard ratio favouring venetoclax with azacitidine over LoDAC (HR 0.46, 95% CI: 0.20, 1.05), but the result was not statistically significant.
- 6.28 The results for remission rates (CR+CRi) in the indirect treatment comparison between venetoclax with azacitidine versus LoDAC, statistically significantly favoured venetoclax with azacitidine (OR 5.94, 95% CI: 2.70, 13.07).
- 6.29 Given the substantial differences between the M15-656 trial and AZA-AML-001 study, the poor transitivity and comparability between studies, and high risk of bias in the open label AZA-AML-001 study, the results of the indirect treatment comparison were highly uncertain, and should be interpreted with caution. The small size of the relevant AZA-001 study subgroups and the high risk of bias in the study added further uncertainty to the indirect treatment comparison, and therefore, the sensitivity analysis including the meta-analysis of AZA-AML-001 and AZA-001 studies was not informative.

#### **Venetoclax with azacitidine vs LoDAC (propensity score weighted analysis)**

- 6.30 The propensity score weighted analysis was based on a logistic regression model of individual patient data (IPD) from the M15-656 (VTX+AZA arm) and M16-043 (LoDAC arm) trials. Baseline covariates were selected based on prognostic factors and potential confounders identified in prior research; i.e. age (< 75, ≥ 75 years), race, gender, geographic region, AML status (de novo, secondary), myelodysplasia related changes, history of MDS, ECOG score, cytogenetic risk category, bone marrow blasts, and prior systemic therapy use. These were appropriate. Region (rest-of-world),

secondary AML and prior systemic therapies were also identified as potential treatment effect modifiers.

- 6.31 The analysis used a fitted Cox proportional hazards model for estimates of overall survival and event free survival, and generalised linear models to estimate remission rates, adjusting for treatment arm. A comparison of patient demographic and disease covariates before and after weighting demonstrated good matching of potential treatment effect modifiers between trials with minimal weighting.
- 6.32 The methodology used in the propensity score weighted analysis was not adequately described. The adjustment of the relative contributions of individual patients across the two cohorts did not affect the effective sample size of the analysis. Although the cohorts were adjusted for prior systemic therapy (yes/no), it is unclear whether this adequately accounted for differences in trial eligibility criteria regarding prior use of HMAs (20.6% in LoDAC arm of Trial M16-043; 0% in venetoclax with azacitidine arm in Trial M15-656 due to exclusion of patients with prior HMA use).
- 6.33 Table 8 shows the results of the propensity score weighted analysis for the outcomes of overall survival and event free survival.

**Table 8: Results for overall survival and event free survival of the propensity score weighted analysis of venetoclax + azacitidine versus LoDAC**

	Propensity score analysis	
	VTX + AZA (N=285)	Pbo + LoDAC (N=66)
<b>Overall survival</b>		
Mean follow-up (months)	12.23	6.76
Patients with event (death), n (%)	161/285 (56.5%)	53/66 (80.3%)
Weighted median time to event, months (95% CI)	14.69 (12.12, 19.45)	7.85 (3.61, 10.18)
Hazard ratio (95% CI)	<b>0.51 (0.36, 0.72)</b>	
Overall survival at 6 month, %	71.93%	55.60%
Overall survival at 12 month, %	56.08%	29.92%
Overall survival at 24 month, %	44.86%	21.58%
<b>Event free survival</b>		
Mean follow-up (months)	10.44	4.56
Patients with event, n (%)	190/285 (66.7%)	58/66 (87.9%)
Weighted median time to event, months (95% CI)	9.89 (8.61, 12.12)	3.12 (1.71, 5.82)
HR (95% CI)	<b>0.39 (0.28, 0.54)</b>	
Event free survival at 6 month, %	68.27%	31.04%
Event free survival at 12 month, %	43.79%	16.29%
Event free survival at 24 month, %	34.95%	9.22%

Source: Table 2-74, p.189 and Table 2-76, p.191 of the submission. Statistically significant results in bold.

Abbreviations: AZA, azacitidine; CI, confidence interval; HR, hazard ratio; LoDAC, low-dose cytarabine; Pbo, placebo; VTX, venetoclax.

- 6.34 In the propensity score weighted analysis, patients treated with venetoclax with azacitidine experienced a statistically significant improvement in overall survival compared to patients treated with LoDAC (HR 0.51, 95% CI: 0.36, 0.72), with an increase in median overall survival of 6.8 months.

- 6.35 Patients treated with venetoclax with azacitidine experienced a statistically significant improvement in event free survival compared to patients treated with LoDAC (HR 0.39, 95% CI: 0.28, 0.54), with an increase in median event-free survival of 6.8 months.
- 6.36 Statistically significantly larger proportions of patients treated with venetoclax with azacitidine achieved complete remission, complete remission with incomplete blood count recovery, and the composite outcome of CR plus CRi.
- 6.37 Given the differences between the inclusion criteria of the M15-656 and M16-043 trials in terms of prior treatment with a HMA (including azacitidine), and the poor documentation of the methodology used in the analysis, the results of the propensity score weighted analysis were uncertain, and should be interpreted with caution.

### Comparative harms

- 6.38 Table 9 summarises the proportions of patients reporting key adverse events in the M15-656 and M16-043 trials.

**Table 9: Summary of treatment emergent adverse events from M15-656 (SAS; Groups 1 & 2) and M16-043 (SAS)**

	M15-656		M16-043	
	VTX + AZA (N=283)	Pbo + AZA (N=144)	VTX + LoDAC (N=142)	Pbo + LoDAC (N=68)
<b>Treatment emergent AEs</b>				
Any adverse event, n (%)	283 (100%)	144 (100%)	141 (99.3%)	67 (98.5%)
Grade ≥3 adverse event, n (%)	279 (98.6%)	139 (96.5%)	138 (97.2%)	65 (95.6%)
Serious adverse event	235 (83.0%)	105 (72.9%)	95 (66.9%)	42 (61.8%)
Adverse event leading to death, n (%)	64 (22.6%)	29 (20.1%)	33 (23.2%)	14 (20.6%)
AE related VTX/Pbo discontin, n (%)	69 (24.4%)	29 (20.1%)	37 (26.1%)	16 (23.5%)
AE related AZA/LoDAC discontin, n (%)	68 (24.0%)	29 (20.1%)	37 (26.1%)	16 (23.5%)
<b>Adverse events of interest</b>				
Tumour lysis syndrome	3 (1.1%)	0 (0%)	8 (5.6%)	0 (0.0%)
Tumour lysis syndrome Grade ≥3	2 (0.7%)	0 (0%)	7 (4.9%)	0 (0.0%)
Serious tumour lysis syndrome	2 (0.7%)	0 (0%)	2 (1.4%)	0 (0.0%)

Source: Table 2-60, p.165 of the submission.

Abbreviations: AE, adverse event; AZA, azacitidine; Discont, discontinued; LoDAC, low intensity cytarabine; Pbo, placebo; SAS, safety analysis set; VTX, venetoclax.

- 6.39 In Trials M15-656 and M16-043, larger proportions of patients treated with venetoclax with azacitidine or venetoclax with LoDAC reported Grade ≥3 adverse events, serious adverse events, adverse events leading to discontinuation and deaths compared to azacitidine or LoDAC monotherapies.
- 6.40 In Trial M15-656, the most frequently reported adverse events of any grade reported by ≥10% of patients were thrombocytopenia (VTX+AZA 51% vs AZA 41%), neutropenia (45% vs 30%), nausea (44% vs 35%), febrile neutropenia (42% vs 19%), diarrhoea (41% vs 33%), and haemorrhage (38% vs 37%).
- 6.41 In Trial M16-043, the most frequently reported adverse events of any grade reported by ≥10% of patients were neutropenia (VTX+LoDAC 53% vs LoDAC 22%), thrombocytopenia (50% vs 46%), nausea (43% vs 31%), haemorrhage (42% vs 31%), diarrhoea (33% vs 18%), and febrile neutropenia (32% vs 29%).

6.42 In Trial M15-656, three patients treated with venetoclax with azacitidine experienced TLS (1.1%). In Trial M16-043, eight patients treated with venetoclax with LoDAC experienced TLS (5.6%), with two TLS-related deaths.

6.43 Table 10 summarises the most frequently reported adverse events Grade  $\geq 3$  experienced by  $\geq 5\%$  of patients in Trials M15-656 and M16-043.

**Table 10: Treatment emergent adverse events of interest and summarised Grade  $\geq 3$  adverse events reported in M15-656 (SAS Group 1 & 2; 4 Jan 2020 cut-off) and M16-043 (SAS; 6 months follow up)**

	M15-656		M16-043	
	VTX + AZA (N=283)	Pbo + AZA (N=144)	VTX + LoDAC (N=142)	Pbo + LoDAC (N=68)
Blood and lymphatic system disorders	233 (82.3%)	98 (68.1%)	111 (78.2%)	50 (73.5%)
Thrombocytopenia	126 (44.5%)	55 (38.2%)	65 (45.8%)	26 (38.2%)
Neutropenia	119 (42.0%)	41 (28.5%)	69 (48.6%)	12 (17.6%)
Febrile neutropenia	118 (41.7%)	27 (18.8%)	46 (32.4%)	20 (29.4%)
Anaemia	74 (26.1%)	29 (20.1%)	38 (26.8%)	15 (22.1%)
Infections and infestations	180 (63.6%)	74 (51.4%)	61 (43.0%)	34 (50.0%)
Pneumonia	56 (19.8%)	36 (25.0%)	31 (21.8%)	11 (16.2%)
Sepsis	17 (6.0%)	13 (9.0%)	8 (5.6%)	4 (5.9%)
Urinary tract infection	11 (3.9%)	8 (5.6%)	10 (7.0%)	1 (1.5%)
Cardiac disorders	44 (15.5%)	20 (13.9%)	13 (9.2%)	11 (16.2%)
Atrial fibrillation	17 (6.0%)	3 (2.1%)	-	-
Gastrointestinal disorders	42 (14.8%)	17 (11.8%)	19 (13.4%)	6 (8.8%)
General disorders, administration site	38 (13.4%)	22 (15.3%)	12 (8.5%)	7 (10.3%)
Injury, poisoning and procedural complications	15 (5.3%)	9 (6.3%)	-	-
Investigations	58 (20.5%)	13 (9.0%)	27 (19.0%)	10 (14.7%)
Metabolism and nutrition disorders	78 (27.6%)	39 (27.1%)	40 (28.2%)	22 (32.4%)
Neoplasms benign, malignant and unspecified	8 (2.8%)	8 (5.6%)	-	-
Nervous system disorders	31 (11.0%)	8 (5.6%)	8 (5.6%)	3 (4.4%)
Renal and urinary disorders	15 (5.3%)	11 (7.6%)	-	-
Respiratory, thoracic and mediastinal disorders	44 (15.5%)	15 (10.4%)	12 (8.5%)	11 (16.2%)
Vascular disorders	36 (12.7%)	12 (8.3%)	17 (12.0%)	7 (10.3%)

Source: Table 2-54, p.156 and Table 2-62, pp.167, Table 2-67, p.174 of the submission.

Abbreviations: AE, adverse event; AZA, azacitidine; CI, confidence interval; MedDRA, Medical Dictionary for Regulatory Activities; PBO, placebo; SAS, safety analysis set; SOC, system organ class; VTX, venetoclax.

Note: MedDRA 21.0 SOC Preferred term.

6.44 Adverse events for Trials AZA-AML-001 and AZA-001 were poorly reported. In the AZA-AML-001 trial, 94.3-99.5% of patients experienced one or more adverse events and the most commonly reported adverse events reported by patients with AML unfit for intensive induction chemotherapy were febrile neutropenia (AZA 26.5% vs LoDAC 30.1%), neutropenia (24.5% vs 24.8%), thrombocytopenia (25.2% vs 27.5%), pneumonia (16.6% vs 19.0%) and anaemia (19.2% vs 22.9%). The most commonly reported adverse events in Trial AZA-001 by patients with AML unfit for intensive induction chemotherapy were neutropenia (AZA 85.7% vs LoDAC 88.9%), thrombocytopenia (92.9% vs 100%) and anaemia (71.4% vs 77.8%).

6.45 Post marketing reports and adverse events reported in clinical trials not included in the submission were consistent with the safety results of the M15-656 and M16-043 trials. The sponsor's current Core Risk Management Plan and the most recent Periodic Safety Update (PSUR) for the reporting period 5 June 2019 – 4 December 2019

identified TLS, neutropenia, and serious infections as important identified risks associated with venetoclax, and embryofetal toxicity, second primary malignancy and toxicity in patients with severe hepatic impairment as important potential risks.

### **Benefits/harms**

- 6.46 On the basis of direct evidence presented in the submission, over a median follow-up of 20.4 months, for every 100 patients treated with venetoclax with azacitidine versus azacitidine:
- Approximately 18 additional patients will be alive at 2 years.
  - Approximately 38 additional patients will experience remission.
  - Approximately 2 additional patients will experience an adverse event leading to death.
  - Approximately 2 additional patients will experience a grade  $\geq 3$  adverse event.
  - Approximately 1 additional patient will experience tumour lysis syndrome.
- 6.47 A benefits/harms summary was not presented for the comparison of venetoclax with azacitidine versus LoDAC given the uncertainty associated with the indirect analysis and the lack of appropriate incremental outcomes over comparable durations of follow-up.

### **Clinical claim**

- 6.48 The submission described venetoclax in combination with azacitidine as superior in terms of effectiveness and inferior in terms of safety compared to with azacitidine or LoDAC monotherapies (all in combination with best supportive care).
- 6.49 The therapeutic conclusions presented in the submission were adequately supported by the clinical evidence presented above. However, the ESC noted the following uncertainties:
- The inclusion criteria of the M15-656 and M16-043 trials presented in the submission may not be applicable to the Australian setting, given differences between the trials and Australian setting in terms of identifying patients unfit for intensive induction chemotherapy, gender, ECOG status, de novo versus secondary AML status, prior therapies for MDS, and baseline cytogenetic risk. The PSCR argued that complementary subgroup analyses presented in the submission did not show any consistent treatment effect modification with respect to OS and EFS, and the treatment effect in each subgroup analysis was consistent with the overall ITT population in both trials. Thus, it considered it unlikely that potential differences between trial participants and patients in Australian clinical practice would impact the relative treatment effect of venetoclax combination therapy.
  - The magnitude of benefit associated with venetoclax with azacitidine compared to LoDAC monotherapy was uncertain given that neither the Bucher indirect

comparison (with substantial differences between M15-656 and AZA-AML-001 trials and poor transitivity) nor the propensity weighted indirect comparison (with poor documentation resulting in uncertainty in whether differences in characteristics were adequately adjusted for) provides a strong basis for assessing relative treatment effects. In the absence of more reliable estimates, it may be reasonable to assume the incremental benefit of venetoclax with azacitidine versus LoDAC monotherapy is similar to the incremental benefit versus azacitidine monotherapy. The PSCR disputed this, stating that the indirect estimate from the Bucher ITC was the most conservative of the indirect analyses and demonstrated a slightly greater incremental OS advantage for venetoclax with azacitidine against LoDAC compared with azacitidine monotherapy.

6.50 The PBAC considered that the claim of superior comparative effectiveness was adequately supported by the data, noting that the magnitude of the benefit was uncertain due to the issues described above.

6.51 The PBAC considered that the claim of inferior comparative safety was reasonable.

### ***Economic analysis***

6.52 The submission presented two economic evaluations:

- a modelled economic evaluation of venetoclax with azacitidine compared to azacitidine, based on extrapolated survival curves from Trial M15-656 and other modelled variables; and
- a modelled economic evaluation of venetoclax with azacitidine and LoDAC, based on an indirect comparison of overall survival (based on M15-656 and AZA-AML-001) and a naïve comparison of event-free survival (based on M15-656 and M16-043) and other modelled variables.

6.53 Azacitidine is currently PBS listed only for patients with myelodysplastic syndrome, chronic myelomonocytic leukaemia, and AML with 20% to 30% marrow blasts who have multi-lineage dysplasia. Azacitidine is a high cost therapy with a similar cost to venetoclax on a monthly basis. The cost-effectiveness of azacitidine as a comparator regimen in the broader proposed PBS population has not been established.

6.54 The submission presented a weighted incremental cost effectiveness ratio (ICER), based on expected substitution of venetoclax with azacitidine for azacitidine and LoDAC in Australian clinical practice. The economic evaluation was presented as a cost utility analysis.

**Table 11: Summary of model structure, key inputs and rationale**

Component	Summary
Treatments	Venetoclax with azacitidine, azacitidine monotherapy, low-dose cytarabine monotherapy (LoDAC)
Time horizon	20 years in the model base case versus median duration of follow-up of 20.5 months in M15-656 and 17.5 months in M16-043
Outcomes	Event-free life years; life years, quality adjusted life years (QALYs)
Methods used to generate results	Partitioned survival analysis
Health states	Event-free; post-event; dead
Cycle length	28 days
Allocation to health states	<p><u>VTX+AZA versus AZA</u></p> <ul style="list-style-type: none"> <li>- Overall survival and event-free survival based on Kaplan-Meier curves from Trial M15-656 for the median duration of follow-up (20×28-day cycles), followed by parametric extrapolation.</li> <li>- 83% of incremental QALYs and 57% of the incremental costs were accrued in the extrapolated period.</li> </ul> <p><u>VTX+AZA versus LoDAC</u></p> <ul style="list-style-type: none"> <li>- Overall survival based on Kaplan-Meier survival curve for VTX+AZA, with LoDAC informed by hazard ratio from indirect comparison between Trials M15-656 and AZA-AML-001; event-free survival based on a naïve comparison of Kaplan Meier curves from Trials M15-656 and M16-043 for median duration of follow-up of Trial M16-043 (18×28-day cycles), followed by parametric extrapolation.</li> <li>- 74% of incremental QALYs and 45% of the incremental costs were accrued in the extrapolated period.</li> </ul>
Health related quality of life	<p>Utilities for event-free disease with CR/CRi (0.807) and event-free disease without CR/CRi (0.740) based on EQ-5D-5L data from Trial M15-656. Based on a mixed effect model, accounting for clustering of values within each patient.</p> <p>Utility for post-event health state (0.623) based on the utility for progressive disease used in the 2016 NICE Technology Appraisal Guidance for azacitidine.</p>
Health resource use and costs	<p>Drug costs based on dose regimens and dose intensity in the key trials. Administration costs based on an assumed split between inpatient (67%) and day stay (33%) hospitalisation in cycle 1; and outpatient administration in subsequent cycles.</p> <p>Adverse event costs based on proportions of patients hospitalised with adverse events and proportions of patients with selected treatment emergent adverse events in the key trials.</p> <p>Costs of TLS prophylaxis and management based on measures recommended in product information.</p> <p>Subsequent treatment costs not included in the economic evaluation.</p> <p>Disease management costs not included in the economic evaluation.</p>

Source: Constructed during the evaluation

Abbreviations: CR, complete remission; CRi, complete remission with incomplete blood count recovery.

- 6.55 A partitioned survival design was implemented to distribute patients between model health states. The overall survival and event-free survival curves derived from Trials M15-656, M16-043 and AZA-AML-001 were used to distribute patients between the model health states.
- 6.56 In the included trials, event-free survival events incorporated death, disease progression, and treatment failure. Thus, the difference between the overall survival and event-free survival curves does not represent disease progression alone, but a mix of disease progression and treatment failure. Therefore, the evaluation and the ESC advice referred to the progressive disease state as a post-event state.
- 6.57 Key drivers of the economic model are summarised in the table below.

**Table 12: Key drivers of the model**

Description	Method/Value	Impact
Azacitidine vials per administration	The dose intensity of azacitidine when used in combination with venetoclax was based on the dose intensity of oral venetoclax in Trial M15-656 (73.2%; dose intensity for azacitidine was not reported in the M15-656 clinical trial report). This resulted in one vial of azacitidine being required per administration. In contrast, the dose intensity of azacitidine when used as monotherapy was based on the dose intensity of placebo tablets (90.4%) and resulted in two vials of azacitidine being required per administration. Overall, it is highly likely that the submission underestimated the dose intensity of azacitidine injections when used in combination with venetoclax. The PSCR acknowledged this, and provided revised ICER calculations (see paragraph 6.68), and the pre-PBAC response provided further analyses (see paragraph 6.77).	High, favours venetoclax + azacitidine
Time horizon	A 20-year time horizon was nominated on the basis that this was appropriate to capture the majority of costs and benefits in an older AML population (baseline age was 75 years in the model). Current AIHW data indicate that 5-year relative survival in AML patients aged 75-79 years old is 7.7% (relative 5-year survival in persons 2012-2016; AIHW 2020 Cancer data in Australia). This suggests that even with a substantial increase in overall survival with venetoclax with azacitidine, the vast majority of patients will have died before 10 years. Therefore a 10-year time horizon may be more appropriate and would reduce the uncertainty associated with longer-term extrapolation of patient survival. The pre-PBAC response presented a scenario with a 15-year time horizon (see Table 17 below).	High, favours venetoclax + azacitidine
Extrapolation	<p>The lognormal function selected to extrapolate overall survival beyond the duration of the key trials resulted in per cycle mortality rates that were lower than Australian general population mortality estimates (for a cohort of patients aged 75-79 years). These overall survival estimates were adjusted to account for age- and sex-specific mortality rates from 24 months, to ensure that overall survival did not exceed general population estimates. Instead, it would be more appropriate to choose an extrapolation function that generated clinically plausible survival estimates compared to the general population. The pre-PBAC response disagreed, but presented a revised scenario with alternative survival estimates (see Table 17 below).</p> <p>The extrapolated overall and event-free survival curves suggest a relatively long duration in the post-event state. This may not be reasonable as the time between treatment failure, progression and death is generally very short in AML patients.</p>	High, favours venetoclax + azacitidine

Source: Constructed during the evaluation

Abbreviations: AML, acute myeloid leukaemia

6.58 Different sources of data informed the LoDAC arm of the economic analysis, with overall survival derived by applying the hazard ratio from the indirect comparison of VTX+AZA (Trial M15-656) versus LoDAC (Trial AZA-AML-001) to the VTX+AZA overall survival curve, and event-free survival informed by a naïve comparison of VTX+AZA (Trial M15-656) and LoDAC (Trial M16-043). Partitioned survival analyses rely on the within-trial relationship between non-mutually exclusive survival curves to determine health state membership. The ESC advised that the use of different sources to derive the overall and event-free survival curves meant that the relationship between overall survival and event-free survival for LoDAC may be due to differences between the different trials informing estimates. Thus, the use of this model structure resulted in a cost-effectiveness estimate that was inherently uncertain. The pre-PBAC response noted that a formal indirect comparison was not possible for event free survival (due to lack of event free survival data in Dombret, 2015), and claimed that the impact of different trial populations on the estimation of overall survival in the indirect comparison would be minimal.

- 6.59 Although the model only had three health states (event-free, post-event, and dead), event-free utility values were based on a post-hoc, mixed-effects regression of EQ-5D-5L utility scores stratified by response status (complete remission, no complete remission) from Trial M15-656, which were applied to the proportions of patients with or without complete remission from Trials M15-656 and M16-043. In the analysis, response status was treated as a constant effect, which is not consistent with available data that indicates that response status changes over time. Based on this analysis, the estimated utility of the event-free state with complete remission was 0.807 and for event free with no complete remission was 0.740. The estimated utility for complete remission and non-complete remission resulted in a utility difference between treatment arms (due to the substantial differences in complete remission rates) favouring venetoclax with azacitidine that was not actually observed in Trial M15-656. Therefore, the validity of these estimates was highly uncertain. The PSCR maintained the approach in the submission was appropriate, and stated that sensitivity analysis showed that the use of standard health state utilities (0.788 for event-free state regardless of CR status) had minimal impact on the ICER (see Table 15).
- 6.60 The submission included the costs of first line drug therapies and administration, TLS prophylaxis and monitoring, and the costs of treating adverse events, but excluded the costs associated with transfusions, subsequent treatment and disease management. The pre-PBAC response considered the submission's approach to be appropriate.
- 6.61 The costs of adverse events were based on the incidence of selected treatment emergent adverse events, and proportions of patients with adverse events leading to hospitalisation. There was no obvious pattern to the selection of treatment emergent events included in the model and the submission did not consider other costs associated with managing adverse events (e.g. use of G-CSF to manage cytopenias). The submission did not adequately justify the use of incidence estimates rather than event rates given the differences in treatment exposure between arms and the potential for patients to experience multiple events. The unit costs associated with adverse events were inadequately justified. The costs associated with adverse events for venetoclax with azacitidine were likely to be substantially underestimated.
- 6.62 The submission and PSCR noted that venetoclax with azacitidine was associated with a statistically significantly higher proportion of patients achieving transfusion independence compared to azacitidine in Trial M15-656 (58.0% vs 33.8%) and argued that the exclusion of transfusion costs did not bias the analysis in favour of venetoclax. Exposure-adjusted transfusion rates indicated that while venetoclax with azacitidine was associated with a decreased rate of infusions compared with azacitidine (1.98 versus 2.69 per 100 patient years), this would be largely offset by the longer time spent on treatment (average duration of treatment in the venetoclax with azacitidine arm was 1.55 years, compared with 0.69 years in the azacitidine arm). Additionally, patients in the venetoclax with azacitidine arm had a longer duration in the post-event

state in the model, in which patients are likely to have higher rates of blood transfusions.

- 6.63 The submission and PSCR argued that patients in the venetoclax with azacitidine arm experience disease progression and death at a later date than patients in the comparator arms, and it assumed that post-event chemotherapy and terminal care costs would be equivalent between treatment arms. This claim was not reasonable, as it did not account for the increased time spent in the post-event state for patients in the venetoclax with azacitidine arm (1.32 years) compared to azacitidine (0.77 years) or LoDAC (0.69 years). Overall, the exclusion of post-event treatment costs was likely to favour venetoclax with azacitidine treatment.
- 6.64 The economic evaluation did not include health state costs (e.g., visits to health care providers, hospitalisations, emergency room visits, tests for disease monitoring). The ESC advised that this was not appropriate, as patients in the venetoclax with azacitidine arm spend more time in the event-free and post-event health states compared to the other treatment arms, and the exclusion of these costs favoured venetoclax with azacitidine. The ESC advised that the exclusion of these costs was inappropriate for a high resource use condition.
- 6.65 The results of the modelled economic evaluation are summarised below.

**Table 13: Results of the economic evaluation**

Component	Venetoclax + azacitidine	Comparator	Increment
<b>VTX+AZA versus AZA</b>			
Costs	\$ [redacted]	\$34,568	\$ [redacted] <sup>1</sup>
QALYs	1.8295	0.9792	0.8503
<b>Incremental cost/QALY gained</b>			\$ [redacted] <sup>2</sup>
<b>VTX+AZA versus LoDAC</b>			
Costs	\$ [redacted]	\$20,028	\$ [redacted] <sup>2</sup>
QALYs	1.8267	0.8849	0.9417
<b>Incremental cost/QALY gained</b>			\$ [redacted] <sup>2</sup>
<b>Weighted economic evaluation (55.6% substitution for AZA/44.4% substitution for LoDAC)<sup>a</sup></b>			
Costs	\$ [redacted]	\$28,106	\$ [redacted] <sup>2</sup>
QALYs	1.8282	0.9373	0.8910
<b>Incremental cost/QALY gained</b>			\$ [redacted] <sup>2</sup>

Source: Table 3-28, p251 of the submission

Abbreviations: AZA, azacitidine; LoDAC, low-dose cytarabine; QALY, quality adjusted life year; VTX, venetoclax

<sup>a</sup> Based on an assumed 50%:50% split between azacitidine and LoDAC, and assuming 10% of patients would remain on LoDAC, the substitution rates are calculated as 55.6% (=50/90) for azacitidine and 44.4% (=40/90) for LoDAC.

Note: The model applied fees and markups as at the time of submission. These fees were updated on 1 January 2021 (and updated fees and markups as per the 7th Community Pharmacy Agreement were presented as a sensitivity analysis in the submission).

The redacted values correspond to the following ranges:

<sup>1</sup> \$45,000 to < \$55,000

<sup>2</sup> \$55,000 to < \$75,000

- 6.66 Based on the economic model presented in the submission, treatment with venetoclax with azacitidine was associated with a cost per QALY gained of \$55,000 to < \$75,000 compared to azacitidine and LoDAC monotherapies for the treatment of AML patients considered unfit for intensive chemotherapy.

- 6.67 The difference in incremental cost between treatment arms was primarily driven by the cost of the venetoclax component, as well as the higher cost of azacitidine used in combination with venetoclax compared with azacitidine and LoDAC monotherapies.
- 6.68 As noted in Table 12, the cost of azacitidine when used in combination with venetoclax was likely a substantial underestimate, due to the inappropriate application of the venetoclax dose intensity to the azacitidine arm. The PSCR acknowledged that applying the dose intensity of venetoclax to concomitant azacitidine may have been inappropriate, and presented a new post hoc analysis of mean dose intensity in Trial M15-656, which showed that dose intensity of azacitidine in the venetoclax with azacitidine arm (89.8%) was slightly lower than for azacitidine monotherapy (96.2%). The PSCR noted that 9% of the model cohort would require only one vial of azacitidine per infusion, assuming a normally distributed Body Surface Area. The PSCR provided revised ICER calculations in the table below.

**Table 14: ICER if <2 vials of AZA are required per infusion in both arms of the model**

	VTX+AZA vs AZA	VTX+AZA vs LoDAC
1.9 AZA vial required per infusion (i.e. 9% have 1 vial and 91% have 2 vials)	\$ [REDACTED] <sup>1</sup>	\$ [REDACTED] <sup>1</sup>

Source: Table 2, PSCR.

The redacted values correspond to the following ranges:

<sup>1</sup> \$75,000 to < \$95,000

- 6.69 The difference in health outcomes was primarily driven by the additional time spent in the event-free health state, associated with better quality of life, for patients treated with venetoclax with azacitidine compared to azacitidine or LoDAC monotherapies. However, the model also generates a substantial difference in post-event survival between treatment arms that was not adequately supported by available data.
- 6.70 As noted in Table 12, the 20-year time horizon may not have been appropriate in an older AML population with co-morbidities. The PSCR argued that a 20-year horizon was consistent with that for blinatumomab in acute lymphoblastic leukemia (July 2016 Public Summary Document (PSD)), and is shorter than the 40 years for midostaurin in transplant eligible patients [in the cohort aged under 60 years] (July 2018 PSD). The ESC noted that blinatumomab was for a different disease, and advised that patients included in the current economic model were substantially older, with multiple comorbidities compared to patients in the midostaurin economic model. Therefore, a shorter time horizon was appropriate. The pre-PBAC argued that a 10-year time horizon was inappropriate, but considered that a 15-year time horizon may be a reasonable basis for a revised model (see below).
- 6.71 As also noted in Table 12, the lognormal function selected to extrapolate overall survival beyond the duration of the key trials resulted in per cycle mortality rates that were lower than Australian general population mortality estimates (for a cohort of patients aged 75-79 years). These estimates were adjusted by Australian general population estimates to ensure that overall survival did not exceed general population

estimates. Instead, the ESC advised that it would be more appropriate to choose an extrapolation function that generated clinically plausible survival estimates compared to the general population. The pre-PBAC response disagreed, but stated that in the interest of facilitating timely patient access, the sponsor considered the treatment-specific parametric functions may be reasonable.

- 6.72 The PBAC noted that the base case cost-effectiveness estimate should not be considered reliable given the uncertainty associated with extrapolation of survival over a 20-year time horizon in an older AML population with multiple comorbidities, the likely underestimate of the cost of azacitidine when used in combination with venetoclax, and the use of parametric functions that produced estimates of survival that were not clinically plausible.
- 6.73 The results of key univariate sensitivity analyses are summarised below.

Table 15: Results of key sensitivity analyses

	VTX+AZA vs AZA			VTX+AZA vs LoDAC		
	Incr. cost	Incr. QALYs	ICER	Incr. cost	Incr. QALYs	ICER
<b>Base case</b>	\$ [redacted]	0.8503	\$ [redacted] <sup>1</sup>	\$ [redacted]	0.9417	\$ [redacted] <sup>1</sup>
<b>Time horizon (base case 20 years)</b>						
5 years	\$ [redacted]	0.5141	\$ [redacted] <sup>2</sup>	\$ [redacted]	0.6180	\$ [redacted] <sup>3</sup>
10 years	\$ [redacted]	0.7433	\$ [redacted] <sup>1</sup>	\$ [redacted]	0.8394	\$ [redacted] <sup>2</sup>
<b>Health state utilities (base case: event-free CR 0.807; event-free no CR 0.740; progressive disease 0.623)</b>						
Event-free utility 0.788 regardless of CR status	\$ [redacted]	0.8336	\$ [redacted] <sup>1</sup>	\$ [redacted]	0.9212	\$ [redacted] <sup>1</sup>
Progressive disease utility 0.706 (from Trial M15-656)	\$ [redacted]	0.8795	\$ [redacted] <sup>1</sup>	\$ [redacted]	0.9721	\$ [redacted] <sup>1</sup>
<b>Azacitidine vials per administration (base case: 1 for VTX+AZA; 2 for AZA)</b>						
50% VTX+AZA and AZA patients require 2 vials, 50% require 1 vial	\$ [redacted]	0.8503	\$ [redacted] <sup>2</sup>	\$ [redacted]	0.9417	\$ [redacted] <sup>2</sup>
100% VTX+AZA and AZA patients require 2 vials	\$ [redacted]	0.8503	\$ [redacted] <sup>2</sup>	\$ [redacted]	0.9417	\$ [redacted] <sup>2</sup>
<b>Administration costs (base case first cycle 67% patients inpatient/33% patients day unit stay; subsequent cycles outpatient administration based on MBS item 13915 \$67.10)</b>						
VTX+AZA inpatient administration during 3-day ramp-up (followed by outpatient administration of azacitidine); AZA outpatient administration for first cycle	\$ [redacted] <sup>2</sup>	0.8503	\$ [redacted] <sup>1</sup>	\$ [redacted]	0.9417	\$ [redacted] <sup>2</sup>
Outpatient administration based on MBS 13950 (\$111.40) <sup>a</sup>	\$ [redacted]	0.8503	\$ [redacted] <sup>1</sup>	\$ [redacted]	0.9417	\$ [redacted] <sup>2</sup>
<b>Adverse events costs (base case: VTX+AZA \$2,522; AZA \$2,083)</b>						
Adverse events costs based on rates of serious haematological events and severe neutropenia/febrile neutropenia events	\$ [redacted]	0.8503	\$ [redacted] <sup>1</sup>	\$ [redacted]	0.9417	\$ [redacted] <sup>1</sup>
<b>Extrapolation of overall survival based on clinically plausible parametric functions (base case: lognormal for both treatment arms; adjustment for Australian mortality rate)</b>						
Exponential for VTX+AZA and LoDAC; exponential for AZA; no adjustment	\$ [redacted]	0.5029	\$ [redacted] <sup>3</sup>	\$ [redacted]	0.5524	\$ [redacted] <sup>4</sup>
Weibull for VTX+AZA and LoDAC; exponential for AZA; no adjustment	\$ [redacted]	0.7246	\$ [redacted] <sup>1</sup>	\$ [redacted]	0.7353	\$ [redacted] <sup>2</sup>
<b>Extrapolation of overall survival and event-free survival based on clinically plausible parametric functions (base case: lognormal for OS for both treatment arms, with adjustment for Australian mortality rate; generalised gamma for EFS for both treatment arms)</b>						
OS: Weibull for VTX+AZA and LoDAC; exponential for AZA; no adj EFS: Weibull VTX+AZA and LoDAC; exponential for AZA	\$ [redacted]	0.6849	\$ [redacted] <sup>1</sup>	\$ [redacted]	0.7152	\$ [redacted] <sup>2</sup>
OS: Weibull for VTX+AZA and LoDAC; exponential for AZA; no adj EFS: exponential VTX+AZA and LoDAC; exponential for AZA	\$ [redacted]	0.6744	\$ [redacted] <sup>1</sup>	\$ [redacted]	0.7062	\$ [redacted] <sup>1</sup>

Source: Table 3-30 of the submission and additional analyses conducted during the evaluation using VTX+AZA AML Economic Evaluation spreadsheet provided with the submission.

Abbreviations: AZA, azacitidine; CR, complete remission; EFS, event-free survival; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; LoDAC, low-dose cytarabine; OS, overall survival; QALY, quality adjusted life year; VTX, venetoclax

<sup>a</sup> MBS item 13915 was replaced with MBS item 13950 from November 2020 (\$111.40; Parenteral administration of antineoplastic agents, including cytotoxic chemotherapy, by or on behalf of a specialist or consultant physician).

The redacted values correspond to the following ranges:

<sup>1</sup> \$55,000 to < \$75,000

<sup>2</sup> \$75,000 to < \$95,000

<sup>3</sup> \$95,000 to < \$115,000

<sup>4</sup> \$115,000 to < \$135,000

6.74 The results of the sensitivity analyses indicated that the model was most sensitive to the number of vials of azacitidine per administration in the venetoclax with azacitidine arm, time horizon, and the parametric functions used to extrapolate overall survival and event-free survival.

6.75 Multivariate sensitivity analyses were conducted during the evaluation, incorporating a 10-year time horizon (given the uncertainty associated with extrapolation of survival over a 20-year time horizon), assuming 2 vials of azacitidine are required per administration when used in combination with venetoclax, and using parametric functions for overall survival and event-free survival informed by clinical plausibility and goodness of fit statistics.

**Table 16: Results of multivariate sensitivity analyses**

	VTX+AZA vs AZA			VTX+AZA vs LoDAC		
	Incr. cost	Incr. QALYs	ICER	Incr. cost	Incr. QALYs	ICER
<b>Base case</b>	\$ [redacted]	<b>0.8503</b>	\$ [redacted] <sup>1</sup>	\$ [redacted]	<b>0.9417</b>	\$ [redacted] <sup>1</sup>
Step 1: 10 year time horizon	\$ [redacted]	0.7433	\$ [redacted] <sup>1</sup>	\$ [redacted]	0.8394	\$ [redacted] <sup>2</sup>
Step 2: as for Step 1, with all VTX+AZA patients requiring 2 vials of azacitidine	\$ [redacted]	0.7433	\$ [redacted] <sup>3</sup>	\$ [redacted]	0.8394	\$ [redacted] <sup>3</sup>
Step 3a: as for Step 2, with clinically plausible extrapolation of OS (Weibull for VTX+AZA; exponential for AZA, no adjustment for Australian mortality rate) and EFS (Weibull for VTX+AZA; exponential for AZA)	\$ [redacted]	0.6533	\$ [redacted] <sup>2</sup>	\$ [redacted]	0.6857	\$ [redacted] <sup>3</sup>
Step 3b: as for Step 2, with clinically plausible extrapolation of OS (Weibull for VTX+AZA; exponential for AZA, no adjustment for Australian mortality rate) and EFS (exponential for VTX+AZA; exponential for AZA)	\$ [redacted]	0.6431	\$ [redacted] <sup>2</sup>	\$ [redacted]	0.6770	\$ [redacted] <sup>3</sup>

Source: Conducted during the evaluation using VTX+AZA AML Economic Evaluation spreadsheet provided with the submission  
 Abbreviations: AZA, azacitidine; CR, complete remission; ICER, incremental cost-effectiveness ratio; LoDAC, low-dose cytarabine QALY, quality adjusted life year; VTX, venetoclax

The redacted values correspond to the following ranges:

<sup>1</sup> \$55,000 to < \$75,000

<sup>2</sup> \$75,000 to < \$95,000

<sup>3</sup> \$95,000 to < \$115,000

6.76 Based on the multivariate sensitivity analyses, the incremental cost per QALY gained ranged from \$75,000 to < \$95,000 for the comparison of venetoclax with azacitidine versus azacitidine, and from \$95,000 to < \$115,000 for the comparison of venetoclax with azacitidine versus LoDAC, for clinically plausible estimates of survival over a 10-year time horizon adjusted for azacitidine vial usage. The ESC considered that these results were more reliable estimates of cost-effectiveness, although it noted that they did not address the issues regarding the exclusion of specific cost items, selection and costing of adverse events, or the application of utility benefits not observed in trial data (see paragraphs 6.59 to 6.64). Moreover, the ICER for the comparison versus LoDAC was informed by an ITC, which limited its reliability.

- 6.77 The pre-PBAC response presented additional analyses with extrapolations as per Step 3b in Table 16, but assuming an average of 1.9 azacitidine vials per infusion, and a 15-year time horizon, which resulted in a weighted ICER of \$75,000 to < \$95,000 per QALY gained (full results shown in Table 17 below). It stated that in this scenario, azacitidine accounted for █% of the overall incremental cost in the direct comparison versus azacitidine monotherapy and █% in the indirect comparison versus LoDAC. It also argued that since azacitidine is in Formulary 2, and subject to price disclosure, the cost-effectiveness of venetoclax with azacitidine in future years would improve (that is, per the scenarios with an assumed 15% price reduction for azacitidine in the table below).
- 6.78 The PBAC noted that using extrapolations as per Step 3a in Table 16, assuming an average of 1.9 azacitidine vials per infusion, and a 10-year time horizon, resulted in a weighted ICER of \$95,000 to < \$115,000 per QALY gained (ICER vs AZA \$75,000 to < \$95,000; ICER vs LoDAC \$95,000 to < \$115,000; weighting of 55.6% azacitidine/44.4% LoDAC).

Table 17: Revised ICER and sensitivity analyses

	VTX+AZA vs AZA		VTX+AZA vs LoDAC		Weighted ICER	
	Current AZA price	15% reduction in AZA price	Current AZA price	15% reduction in AZA price	Current AZA price	15% reduction in AZA price
<b>ICER presented in PSCR:</b> 20-year time horizon <sup>a</sup> 1.9 AZA vials per infusion Lognormal for OS <sup>a</sup> All-cause mortality adjustment <sup>a</sup>	\$ [redacted] <sup>1</sup>	\$ [redacted] <sup>1</sup>	\$ [redacted] <sup>1</sup>	\$ [redacted] <sup>1</sup>	\$ [redacted] <sup>1</sup>	\$ [redacted] <sup>1</sup>
<b>Step 3b, Table 16 above, multivariate:</b> 10-year time horizon 2 AZA vials per infusion Clinically plausible extrapolation of OS (Weibull for VTX+AZA; exponential for AZA, no adjustment for Australian mortality rate) and EFS (exponential for VTX+AZA; exponential for AZA)	\$ [redacted] <sup>1</sup>	\$ [redacted] <sup>c,1</sup>	\$ [redacted] <sup>2</sup>	\$ [redacted] <sup>c,2</sup>	\$ [redacted] <sup>2</sup>	\$ [redacted] <sup>c,1</sup>
<b>Revised multivariate analysis:</b> 15-year time horizon 1.9 AZA vials per infusion Clinically plausible extrapolation of OS (Weibull for VTX+AZA; exponential for AZA, no adjustment for Australian mortality rate) and EFS (exponential for VTX+AZA; exponential for AZA) <sup>b</sup>	\$ [redacted] <sup>1</sup>	\$ [redacted] <sup>1</sup>	\$ [redacted] <sup>2</sup>	\$ [redacted] <sup>1</sup>	\$ [redacted] <sup>1</sup>	\$ [redacted] <sup>1</sup>

Source: adapted from Table 1, pre-PBAC response.

Abbreviations: AZA = azacitidine; ICER = incremental cost-effectiveness ratio; LoDAC = low-dose cytarabine; PSCR = Pre-Sub-Committee Response; VTX = venetoclax.

<sup>a</sup> As per submission.

<sup>b</sup> Extrapolations as per Step 3b, Table 16 above.

<sup>c</sup> Calculated for the pre-PBAC response.

The redacted values correspond to the following ranges:

<sup>1</sup> \$75,000 to < \$95,000

<sup>2</sup> \$95,000 to < \$115,000

### Drug cost/patient/course

6.79 Drug costs per patient per course of venetoclax with azacitidine, azacitidine monotherapy, and LoDAC monotherapy were estimated based on circumstances of use in the M15-656 and M16-043 trials, the proposed effective price for venetoclax and published prices for azacitidine and LoDAC, and mean duration of treatment from the economic model (see table below). This approach to estimating the cost was consistent across the economic analysis and financial estimates. However, the application of costs differed between the economic and financial analyses. In the economic model, drug costs were based on a cohort of patients receiving different durations of treatment, with a mean duration of 20.17 cycles for venetoclax with

azacitidine. In the financial estimates, all patients were assumed to receive the mean duration of treatment (20.17 cycles for venetoclax with azacitidine) and therefore received treatment over a condensed period of time.

**Table 18: Drug cost per patient per course for venetoclax with azacitidine versus azacitidine or LoDAC monotherapy**

	Venetoclax + azacitidine		Azacitidine monotherapy	LoDAC monotherapy
	Venetoclax	Azacitidine		
Dosing regimen, continued until disease progression	Cycle 1: 100 mg Day 1, 200 mg Day 2, 400 mg Days 3-28; Cycle 2+: 400 mg/day Days 1-28.	75 mg/m <sup>2</sup> daily, Days 1-7	75 mg/m <sup>2</sup> daily, Days 1-7	20 mg/m <sup>2</sup> daily, Days 1-10
Dose intensity	73.2% <sup>a</sup>	73.2% <sup>a</sup>	90.4% <sup>b</sup>	98.6% <sup>c</sup>
Dose per administration	Cycle 1: 7,832.4 mg/cycle <sup>d</sup> Cycle 2+: 8,198.4 mg/cycle <sup>e</sup>	99.4 mg <sup>f</sup>	122.7 mg <sup>g</sup>	35.7 mg <sup>h</sup>
Packs/vials per 28-day cycle	Cycle 1: 0.6527 packs <sup>i</sup> Cycles 2+: 0.6832 packs <sup>j</sup>	7 vials <sup>k</sup>	14 vials <sup>l</sup>	10 vials <sup>m</sup>
Cost/script	\$ [REDACTED] (effective) for 120×100 mg tablets	\$2,192.54 (public) \$2,240.32 (private) for 14×100 mg vials	\$2,192.54 (public) \$2,240.32 (private) for 14×100 mg vials	\$199.75 (public) \$241.99 (private) for 10×100 mg vials <sup>n</sup>
Cost/cycle	Cycle 1: \$ [REDACTED] Cycles 2+: \$ [REDACTED]	\$1,105.60 <sup>o</sup>	\$2,211.20 <sup>p</sup>	\$216.25 <sup>p</sup>
Mean duration of treatment	20.17 cycles <sup>q</sup>	20.17 cycles <sup>q</sup>	8.93 cycles <sup>r</sup>	7.39 cycles <sup>s</sup>
Cost/pt/course	\$ [REDACTED]	\$22,297.72	\$19,750.26	\$1,597.53
<b>Total cost/pt/course</b>	<b>\$ [REDACTED]</b>		<b>\$19,750.26</b>	<b>\$1,597.53</b>

Source: Constructed during the evaluation based on the VTX+AZA AML Economic Evaluation spreadsheet provided with the submission  
Abbreviations: AEMP, approved ex-manufacturer price; AZA, azacitidine; BSA, body surface area; DPMQ, dispensed price for maximum quantity; EFC, efficient funding of chemotherapy; LoDAC, low-dose cytarabine; pt, patient; VTX, venetoclax.

<sup>a</sup> based on dose intensity for venetoclax tablets, accounting for dose reduction and interruption, from Trial M15-656

<sup>b</sup> based on dose intensity for placebo tablets, accounting for dose reduction and interruption, from Trial M15-656

<sup>c</sup> based on dose intensity for placebo tablets, accounting for dose reduction and interruption, from Trial M16-043

<sup>d</sup> Cycle 1 total dose of 10,700 mg (1×100 mg + 1×200 mg + 26×400 mg) multiplied by dose intensity of 73.2%

<sup>e</sup> Cycle 2+ total dose of 11,200 mg (28×400 mg) multiplied by dose intensity of 73.2%

<sup>f</sup> 75 mg/m<sup>2</sup> × 1.81 (BSA from Trial M15-656) × 73.2%

<sup>g</sup> 75 mg/m<sup>2</sup> × 1.81 (BSA from Trial M15-656) × 90.4%

<sup>h</sup> 20 mg/m<sup>2</sup> × 1.81 (BSA from Trial M15-656) × 98.6%

<sup>i</sup> 7,832.4 mg divided by the number of mg of venetoclax per pack (120 × 100 mg)

<sup>j</sup> 8,198.4 mg divided by the number of mg of venetoclax per pack (120 × 100 mg)

<sup>k</sup> 1×100 mg vial per day for 7 days

<sup>l</sup> 1×100 mg vial per day for 7 days

<sup>m</sup> 1×100 mg vial per day for 10 days

<sup>n</sup> based on an AEMP for 5 vials \$56.95; assuming one set of EFC mark-ups are applied per cycle (10 vials); \$199.76 (\$56.96 × 2 + \$85.78) for public hospital; \$241.99 (\$56.96 × 2 + \$126.41)

<sup>o</sup> based on DPMQ for public hospitals × 61% use + DPMQ for private hospitals × 39% use divided by 2 to derive cost of 7 vials. Use in public/private hospitals based on PBS script data for azacitidine

<sup>p</sup> distribution of use in public (61%)/private (39%) hospitals based on PBS script data for azacitidine

<sup>q</sup> based on average time on treatment from the VTX+AZA arm of the economic model

<sup>r</sup> based on average time on treatment from the AZA arm of the economic model

<sup>s</sup> based on average time on treatment from the LoDAC arm of the economic model

6.80 The drug cost per patient per course was \$ [REDACTED] for venetoclax with azacitidine, based on the assumption that only one vial of azacitidine is required per administration. This was based on the dose intensity for venetoclax, which was not appropriate given differences between the components of the dosing regimen in the

number of treatment days per cycle and method of administration, and data from M15-656 indicating that the average number of dosed treatment days per cycle was higher for azacitidine injections (6.9/7 days) compared to venetoclax tablets (23.4/28 days). A dose intensity of 73.7% or higher (compared with 73.2% used to derive the cost of azacitidine) would result in the need for two vials of azacitidine per administration, doubling the azacitidine component costs for venetoclax with azacitidine. If two vials of azacitidine are required per administration, the cost of the azacitidine component becomes \$44,595 and the cost per patient per course of venetoclax with azacitidine increases to \$[REDACTED]. The PSCR acknowledged that the applied dose intensity was inappropriate (see paragraph 6.68).

### ***Estimated PBS usage & financial implications***

- 6.81 This submission was considered by DUSC. The submission used an epidemiological approach to estimate the utilisation and financial impact of listing venetoclax with azacitidine for the treatment of acute myeloid leukaemia. Key inputs are summarised in the table below. The PBAC noted and agreed with the uncertainties identified with regard to these inputs.
- 6.82 DUSC considered the estimates presented in the submission to be underestimated. The main issues were:
- A large underestimate of the number of azacitidine vials required for treatment with venetoclax + azacitidine.
  - There may be leakage into an additional group of patients who are fit for standard intensive remission induction chemotherapy but may choose the less intensive venetoclax with azacitidine chemotherapy (noting that the uptake would depend on how clinicians view the efficacy and safety of venetoclax with azacitidine as there is no consensus on criteria for unfit for standard intensive remission induction chemotherapy in the clinical guidelines and the literature, and the proposed restriction did not include further criteria).
  - An overestimate of the proportion of patients unfit for standard intensive remission induction chemotherapy who receive treatment with venetoclax. (80%, inconsistent with Australian data provided in the submission that suggested a much lower proportion of patients going on to treatment (54%, retrospective review of unfit Australian AML patients in the CURRENT study)).

**Table 19: Key inputs for financial estimates**

Parameter	Value applied and source	Comment
Incidence of AML	4.3 cases per 100,000 population based on AIHW 2020 Cancer Data	The data source was appropriate; however, the submission did not justify the use of average age-specific incidence (4.3) instead of age-standardised incidence (3.8).
Proportion of patients unfit for intensive chemotherapy	50% based on expert opinion (not provided), supported by analysis of AML incidence by age (AIHW 2020 Cancer Data) and a retrospective observational study of patient fitness from Northern Italy (Borlenghi 2014; abstract only)	The proportion of patients who are unfit for intensive chemotherapy is inherently uncertain and is likely to change depending on AML subtypes and the availability of new therapies such as venetoclax.
Proportion of unfit patients who receive treatment	80% based on expert opinion	The estimate was inconsistent with Australian data provided in the submission, which suggested a much lower proportion of patients going on to treatment (54%, retrospective review of unfit Australian AML patients, CURRENT study).
Venetoclax uptake rate	90% based on assumption	While it might be reasonable to assume a high uptake of venetoclax with azacitidine in the target population, the exact proportion was uncertain.
Treatment duration of venetoclax with azacitidine	20.1 cycles based on economic model	The uncertainty associated with survival and time on treatment extrapolations as noted for the economic model apply. The budget impact analysis was inconsistent with the economic model as it condensed treatment duration into the first and second years while the model included patients remaining on treatment in subsequent years.
Treatment duration of azacitidine monotherapy	8.9 cycles based on economic model	
Treatment duration of LoDAC monotherapy	7.4 cycles based on economic model	
Dose intensity of venetoclax with azacitidine	73.2% based on M15-656 trial	It was not appropriate to estimate dose intensity for azacitidine (in combination with venetoclax) based on the use of an oral tablet. The available data suggest that dose intensity is higher for the injectable therapies. The underestimation of azacitidine dose intensity had a major effect on the budget impact analysis as it reduced the number of azacitidine vials from 2 to 1 per administration.
Use of substituted therapies	50% azacitidine monotherapy, 50% LoDAC monotherapy based on retrospective review of unfit Australian AML patients (CURRENT study)	The market share estimates did not account for: - The estimated proportion of unfit patients remaining on LoDAC therapy (10%; used to inform uptake estimates), - The proportion of patients using non-PBS azacitidine (azacitidine PBS population is a subset of the proposed venetoclax PBS population) - The proportion of patients using azacitidine or LoDAC combination regimens (31%, CURRENT study)  The submission did not justify the assumption of equal substitution given azacitidine is PBS listed for a population with limited overlap with the requested population.

Source: compiled during the evaluation

Abbreviations: AIHW, Australian Institute of Health and Welfare; AML, acute myeloid leukaemia; LoDAC, low-dose cytarabine; MDS, myelodysplastic syndrome; PBS, Pharmaceutical Benefits Scheme

6.83 The table below presents the estimated use and financial implications of listing venetoclax with azacitidine over 6 years of listing, based on the proposed effective price of venetoclax.

**Table 20: Estimated use and financial implications**

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Total treated patients	1	1	1	1	1	1
Venetoclax scripts	2	3	3	3	3	3
Azacitidine vials	4	5	5	5	6	6
Total venetoclax with azacitidine cost (less copay)	\$ 7	\$ 8	\$ 8	\$ 8	\$ 8	\$ 8
Azacitidine monotherapy substitution (less copay)	-\$ 9	-\$ 9	-\$ 9	-\$ 9	-\$ 9	-\$ 9
LoDAC monotherapy substitution (less copay)	-\$ 9	-\$ 9	-\$ 9	-\$ 9	-\$ 9	-\$ 9
<b>Net PBS/RPBS cost</b>	\$ 10	\$ 7	\$ 7	\$ 7	\$ 7	\$ 7
Change in MBS costs for administration and monitoring	\$ 9	\$ 9	\$ 9	\$ 9	\$ 9	\$ 9
<b>Net cost to Government</b>	\$ 7	\$ 7	\$ 7	\$ 7	\$ 7	\$ 7

Source: Source: Table 4-4, Table 4-8, Table 4-16, Table 4-19, and Table 4-20 of the submission

Abbreviations: LoDAC, low-dose cytarabine; PBS, Pharmaceutical Benefits Scheme; RPBS, Repatriation Pharmaceutical Benefits Scheme

The redacted values correspond to the following ranges:

<sup>1</sup> < 500

<sup>2</sup> 500 to < 5,000

<sup>3</sup> 5,000 to < 10,000

<sup>4</sup> 30,000 to < 40,000

<sup>5</sup> 50,000 to < 60,000

<sup>6</sup> 60,000 to < 70,000

<sup>7</sup> \$20 million to < \$30 million

<sup>8</sup> \$30 million to < \$40 million

<sup>9</sup> \$0 to < \$10 million

<sup>10</sup> \$10 million to < \$20 million

6.84 Using the proposed effective price of venetoclax, the net PBS/RPBS cost of venetoclax with azacitidine was estimated to be \$20 million to < \$30 million in the sixth year of listing, with a total cost of \$100 million to < \$200 million over six years. The net cost to Government (including MBS costs for administration and monitoring) was \$100 million to < \$200 million over six years.

### Quality Use of Medicines

6.85 The submission stated the sponsor's intent to conduct quality use of medicines activities to support the listing of venetoclax with azacitidine for the treatment of acute myeloid leukaemia.

6.86 DUSC considered that:

- As treatment is a combination of self-administered oral venetoclax and medically supervised injection of azacitidine, there will need to be education for patients and families on administration and disposal of venetoclax, home monitoring and support to ensure adherence to treatment.

- There needs to be additional information and advice for those patients with secondary AML.
- If venetoclax is co-administered with strong or moderate CYP3A inhibitors, dose reductions are recommended to reduce the risk of tumour lysis syndrome (TLS). The submission anticipated that patients receiving CYP3A inhibitors would initiate venetoclax as inpatients. QUM issues for General Practitioners were not discussed in the submission.
- Venetoclax has potential medication interactions with warfarin, CYP3A4 and P-gp inhibitors/inducers, OATP1B1/1B3 inhibitors, azithromycin and gastric acid-reducing agents.

### **Financial Management – Risk Sharing Arrangements**

- 6.87 The PBAC considered that a Risk Sharing Arrangement would be necessary to manage the risk of use in patients previously considered fit for standard intensive remission induction chemotherapy, as the cost-effectiveness is unknown in these patients.

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

## **7 PBAC Outcome**

- 7.1 The PBAC did not recommend venetoclax for the treatment of patients with previously untreated acute myeloid leukaemia (AML) who are ineligible for standard intensive remission induction chemotherapy. The PBAC considered that the combination of venetoclax with azacitidine offered a meaningful clinical improvement, but that the incremental cost-effectiveness ratio (ICER) was high, and for the comparison with LoDAC uncertain, and that a price reduction would be needed to achieve a cost-effective listing. In addition, the PBAC considered there was a high risk of use in patients previously considered eligible for intensive therapy and a Risk Sharing Arrangement (RSA) was required to manage this risk.
- 7.2 In terms of the clinical place for the proposed therapy, the PBAC agreed with the submission that venetoclax with azacitidine would be used as an alternative to low intensity azacitidine or low-dose cytarabine (LoDAC). The PBAC noted that the first-line positioning was consistent with the provisionally approved TGA indication. The PBAC also noted that the TGA Product Information provided dosing instructions for venetoclax combined with either azacitidine or LoDAC, and there is a phase 3 study of venetoclax with LoDAC versus LoDAC (M16-043); however, the submission requested PBS listing for use in combination with azacitidine only. The PBAC considered there would be a patient population in Australia who would use this combination if it were available.
- 7.3 The PBAC noted that the requested listing did not define ineligibility for standard intensive remission induction chemotherapy. The PBAC agreed with the ESC and DUSC

that there is no consensus definition available, and considered that eligibility would be determined according to clinician judgement and patient preference.

- 7.4 The submission requested an Authority Required (Telephone/Online) listing for venetoclax, but did not include proposals for the combination azacitidine listing. Azacitidine for AML is currently listed on the PBS as a Written Authority for initial treatment and a Telephone/Online Authority for continuation. The PBAC recalled that in November 2020, it had recommended the Authority level for azacitidine for AML be decreased to Authority Required (Telephone) for initial treatment and Authority Required (Streamlined) for continuing (PBAC Outcomes, Other Matters, November 2020). Thus, the PBAC had no concern with the proposed venetoclax and azacitidine combination listings both being Authority Required (Telephone/Online).
- 7.5 The submission requested a maximum quantity of one pack, with five repeats. The PBAC noted that two repeats would provide for three months' supply, which it considered was more in line with the timeframe in which patients should be reviewed.
- 7.6 The submission nominated azacitidine monotherapy as the main comparator, and LoDAC as a secondary comparator (with a 55.6%/44.4% split in the economic evaluation; and 50%/50% market share in the financial estimates). The PBAC considered that the current azacitidine PBS listing for AML (for patients with 20-30% bone marrow blasts and multi-lineage dysplasia) had limited overlap with the requested PBS population, and consequently LoDAC was likely to be the PBS therapy most replaced in practice. Thus, the PBAC agreed with the ESC that while a mixed comparator was appropriate, it should be weighted towards LoDAC.
- 7.7 The main clinical evidence presented in the submission consisted of: a direct comparison of venetoclax with azacitidine versus azacitidine, based on one head-to-head randomised trial (M15-656); and an indirect treatment comparison (ITC) of venetoclax with azacitidine (M15-656) versus LoDAC (AZA-AML-001) with azacitidine as a common reference. For the LoDAC comparison, the submission also presented: an ITC of venetoclax with azacitidine (M15-656) versus LoDAC (meta-analysis of AZA-AML-001 and AZA-001) with azacitidine as a common reference as a sensitivity analysis; and a propensity score weighted analysis of venetoclax with azacitidine (M15-656) versus LoDAC (M16-043) as a supporting analysis. Whilst the PBAC considered the azacitidine comparison was largely reliable (noting some minor uncertainty with respect to applicability to the Australian population), the LoDAC comparisons were less reliable for reasons discussed in the paragraph below.
- 7.8 Overall, the PBAC considered that the claim of superior comparative effectiveness was adequately supported by the data, although the magnitude of the benefit was uncertain:
- For the azacitidine comparison, the PBAC noted that patients treated with venetoclax with azacitidine experienced a statistically significant improvement in overall survival (OS) (HR 0.66, 95% CI: 0.52, 0.85), with an increase in median OS of 5.1 months over a median follow up of 20.4 months. The PBAC considered that

results were consistently favourable towards venetoclax with azacitidine with respect to event free survival (EFS), complete remission (CR), the composite of complete remission and complete remission with incomplete blood count recovery (CR + CRi), and patients achieving red blood cell and/or platelet transfusion independence. Although the PBAC noted that there were no significant Quality of Life differences between the regimens, the PBAC considered that the survival benefits represented a clinically meaningful improvement.

- For the main LoDAC ITC, the PBAC noted that patients treated with venetoclax with azacitidine experienced a statistically significant improvement in OS (HR 0.60, 95% CI: 0.42, 0.85), and also with respect to CR + CRi. The supplementary ITC which meta-analysed AZA-AML-001 and AZA-001 also favoured venetoclax with azacitidine. However, the PBAC considered that there was poor transitivity between the studies in the ITCs, and its assessment of the supplementary ITC was limited by insufficient information provided about the trials. Furthermore, whilst the propensity score weighted analysis was also favourable, its methodology was poorly documented and hence largely uninformative.

- 7.9 The submission claimed that venetoclax with azacitidine had inferior safety compared with azacitidine or LoDAC, which the PBAC considered was reasonable in view of the larger proportions of patients treated with venetoclax with azacitidine experiencing Grade  $\geq 3$  adverse events, serious adverse events, adverse events leading to discontinuation and deaths compared to azacitidine, as well as the other safety information presented in paragraphs 6.39 - 6.45.
- 7.10 The submission presented partitioned survival analyses comparing venetoclax with azacitidine against the two comparators, resulting in a weighted incremental cost effectiveness ratio (ICER) of \$55,000 to < \$75,000 per QALY gained (ICER vs azacitidine \$55,000 to < \$75,000 ; ICER vs LoDAC \$55,000 to < \$75,000; 55.6%/44.4% split respectively). The PBAC considered that this base case estimate was unreliable due to the issues discussed in Table 12 (azacitidine vials per administration, the time horizon and extrapolation), and also noted the issues with the costing and utility inputs discussed in paragraph 6.59 to 6.64. In addition, the ICER was weighted towards azacitidine, which was not the appropriate main comparator, and the clinical inputs for the LoDAC comparison meant that the partitioned survival analysis was inherently uncertain (see paragraph 6.58).
- 7.11 The PBAC noted that the pre-PBAC response provided a revised multivariate sensitivity analysis with extrapolations as per Step 3b in Table 16, but assuming an average of 1.9 azacitidine vials per infusion, and a 15-year time horizon, resulting in a weighted ICER of \$75,000 to < \$95,000 per QALY gained. The PBAC considered that the vial assumption was reasonable, but that more conservative extrapolations (per Step 3a) and a 10-year time horizon were appropriate in view of the inherent uncertainty associated with the ITC versus LoDAC, as well as the other unaddressed issues with the model (i.e. costings and utilities). The PBAC noted that this scenario resulted in an

ICER vs azacitidine of \$75,000 to < \$95,000 and an ICER vs LoDAC of \$95,000 to < \$115,000. The PBAC considered that an ICER of approximately \$60,000 to \$80,000 per QALY gained would likely be acceptable, and noted that a price reduction for venetoclax would be needed to achieve this ICER.

- 7.12 In terms of the estimated PBS usage and financial implications, the PBAC agreed with DUSC that the number of vials of azacitidine had been underestimated and the proportion of patients unfit for standard intensive regimens had been overestimated. The PBAC agreed with both the DUSC and ESC that uptake would depend on how clinicians view the efficacy and safety of venetoclax with azacitidine, as there is no consensus on criteria for unfitness for standard intensive remission induction chemotherapy in clinical guidelines or the literature. The PBAC considered that patients whose eligibility for a curative regimen was currently “borderline” would likely seek treatment with venetoclax once listed on the PBS. The PBAC considered that a Risk Sharing Arrangement would be necessary to manage the risk of uptake in these patients in which cost-effectiveness has not been established.
- 7.13 The PBAC considered the outstanding issues may be addressed in a simple resubmission for venetoclax if the following changes were made, without any additional amendments to the economic evaluation or financial implications:
- A price reduction such that economic model resulted in an ICER of approximately \$75,000 to <\$95,000 for the scenario described in paragraph 7.11 (that is, an average of 1.9 azacitidine vials per infusion, extrapolations as per Step 3a of Table 16, and a 10-year time horizon), with the ICER weighted towards the LoDAC comparison.
  - Revisions to the estimated financial implications: applying the lower price noted in the point above; amending the dose intensity of azacitidine when used in combination with venetoclax to reflect M15-656 evidence; and reducing the estimate of the proportion of patients unfit for intensive regimens who receive treatment for venetoclax (from 80% in the submission).
  - Outline an RSA to manage risk of use in patients previously considered fit for standard intensive remission reduction regimens.
- 7.14 The PBAC considered an early re-entry pathway would be acceptable if the resubmission addressed each of the points in the above paragraph with no further adjustment. The resubmission must be lodged by week 7 of the current PBAC cycle or at the standard due date for PBAC submissions for the next cycle. If any of these terms are not acceptable to the sponsor, a standard re-entry pathway is available.
- 7.15 The PBAC noted that this submission is eligible for an Independent Review.

**Outcome:**  
Rejected

## **8 Context for Decision**

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

## **9 Sponsor's Comment**

AbbVie welcomes the PBAC's acknowledgement that venetoclax + azacitidine provides a meaningful clinical improvement for patients with AML. AbbVie will continue to work collaboratively with the PBAC to seek access for patients in this area of high unmet need