

An addendum to this Public Summary Document has been included at the end of the document.

Changes have been made to this item. Details of the corrigendum are at the end of this document.

**5.03 AZACITIDINE,  
Tablet 200 mg, Tablet 300 mg,  
Onureg<sup>®</sup>,  
Celgene Pty Limited.**

**1 Purpose of submission**

- 1.1 The Category 2 submission requested a Section 85 (General Schedule) Authority Required (Streamlined) listing for oral azacitidine as maintenance therapy in patients with acute myeloid leukaemia (AML) who achieve complete remission (CR) or complete remission with incomplete blood count recovery (CRi) following induction chemotherapy with or without consolidation treatment, and who are not candidates for, including those who choose not to proceed to, haematopoietic stem cell transplantation (HSCT). Oral azacitidine has not previously been considered by the PBAC for this indication.
- 1.2 Listing was requested on the basis of a cost-utility analysis (CUA) comparing oral azacitidine with best supportive care (BSC), based on the efficacy and safety results from the QUAZAR trial. The key components of the clinical issue addressed by the submission are presented in Table 1.

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

| <b>Component</b> | <b>Description</b>  |
|------------------|---|
| Population       | Adult patients with AML who achieve CR or CRi following induction therapy with or without consolidation treatment, and who are not candidates for, including those who choose not to proceed to HSCT. |
| Intervention     | Azacitidine 300 mg orally QD. Each repeated cycle consists of a treatment period of 14 days followed by a treatment-free period of 14 days (28-day treatment cycle).                                  |
| Comparator       | BSC or no maintenance therapy.  |
| Outcomes         | Primary: OS<br>Key secondary: RFS, TTR, TTD, HRQoL, safety.   |
| Clinical claim   | Compared with BSC or no active treatment, oral azacitidine offers superior comparative efficacy and inferior, but manageable, comparative safety and maintains HRQoL.                                 |

Source: Table 1, p7 of the submission.

Abbreviations: AML = acute myeloid leukaemia; BSC = best supportive care; CR = complete remission; CRi = complete remission with incomplete blood count recovery; HRQoL = health-related quality of life; HSCT = haematopoietic stem cell transplantation; OS = overall survival; QD = quaque die (one a day); RFS = relapse-free survival; TTD = time to discontinuations; TTR = time to relapse.

## **2 Background**

### ***Registration status***

2.1 The submission was made under the TGA/PBAC Parallel Process. The TGA review was conducted via Project Orbis. Oral azacitidine was TGA registered on 8 April 2022 (during the evaluation) for:

‘continued treatment of adult patients with acute myeloid leukemia who achieved first complete remission (CR) or complete remission with incomplete blood count recovery (CRi) following intensive induction chemotherapy and are not able to complete intensive curative therapy’.

2.2 Oral azacitidine was approved by the United States Food and Drug Authority (FDA) on 1 September 2020; the FDA-approved indication is the same as the TGA-approved indication.

2.3 During the TGA approval process, the TGA Delegate noted the FDA Reviewer’s opinion that no firm conclusions could be drawn regarding the efficacy of treatment with oral azacitidine for patients who had completed 3 cycles of consolidation. The TGA Delegate further noted on the basis of data from QUAZAR (see Table 6) that the benefit of maintenance therapy accrues predominantly in patients who have completed no, 1 or 2 cycles of consolidation treatment. The TGA Delegate considered it uncertain if there was any benefit of maintenance therapy in patients who have had 3 rounds of consolidation therapy in whom, allowing for differences of practice, it could be concluded that curative treatment has been completed. Based on this, the Delegate recommended the above TGA approved indication for oral azacitidine (rather than the original proposed TGA indication, which was closely aligned with the proposed PBS listing, that is, for use in adult patients with AML who achieved CR or CRi following induction with or without consolidation treatment and who are not candidates for, including those who choose not to proceed to HSCT).

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

### 3 Requested listing

3.1 The restriction proposed by the submission is outlined below, with amendments proposed in the Pre-Sub-Committee Response (PSCR) shown with strikethrough for deletions, and italics for additions. This includes a reduction in the maximum quantity. The DPMQ has been updated accordingly.

| Name, Restriction, Manner of administration and form | Max. Qty (units)   | No. of Rpts | DPMQ                                     | Proprietary Name and Manufacturer |
|--|--|-------------|--|-----------------------------------|
| Azacitidine<br>300 mg tablet, 7                      | 24 14  | 2           | Published: \$20,574.24<br>Effective: \$█ | Onureg® Celgene Pty Limited       |
| Azacitidine<br>200 mg tablet, 7                      | 24 14  | 2           | Published: \$20,574.24<br>Effective: \$█ | Onureg® Celgene Pty Limited       |
| <b>Category/Program:</b>                             | GENERAL – General Schedule (Code GE)   |             |  |                                   |
| <b>PBS indication:</b>                               | <del>Maintenance</del> Acute Myeloid Leukaemia   |             |  |                                   |
| <b>Restriction:</b>                                  | <input checked="" type="checkbox"/> Streamlined  |             |  |                                   |
| <b>Treatment phase:</b>                              | Initial  |             |  |                                   |
| <b>Clinical criteria:</b>                            | Patient must have demonstrated complete remission or complete remission with incomplete blood count recovery following standard remission induction chemotherapy with or without consolidation treatment,<br>AND<br>Patient must not be a candidate for, including those who choose not to proceed to, haematopoietic stem cell transplantation. |             |  |                                   |
| <b>Population criteria:</b>                          | <del>Adult patients</del>  |             |  |                                   |
| <b>Treatment phase:</b>                              | Continuing   |             |  |                                   |
| <b>Clinical criteria:</b>                            | Patient must have previously received PBS-subsidised treatment with this drug for this condition,<br>AND<br><del>Patient must not have progressive disease. Patient must not have &gt; 15% blasts in the bone marrow or peripheral blood not attributable to any other cause than AML.</del>   |             |  |                                   |
| <b>Treatment criteria:</b>                           | <del>Progressive disease is defined as &gt; 15% blasts in the bone marrow or peripheral blood not attributable to any other cause.</del>   |             |  |                                   |
| <b>Population criteria:</b>                          | <del>Adult patients</del>  |             |  |                                   |
| <b>Administrative advice:</b>                        | <i>An increased maximum quantity of the 300 mg strength may be requested for patients with 5% to 15% blasts in the peripheral blood or bone marrow in order to extend the dose schedule as per the TGA Product Information.</i>  |             |  |                                   |

Source: Table 24, p38; Table 25, p42 and Attachment 1 Restriction template of the submission; PSCR p2.  
Abbreviations: mg = milligram

3.2 The submission sought a special price arrangement (SPA) for oral azacitidine, with a price rebate of approximately █%.

3.3 The submission proposed a General Schedule listing, reasoning that oral azacitidine is administered orally and can be commenced outside a hospital setting. An Authority Required (Streamlined) listing was requested given that eligible patients would have been previously diagnosed with AML and received treatment with induction

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chemotherapy agents (e.g. cytarabine/idarubicin), which are listed on the PBS without an Authority requirement.

- 3.4 The ESC noted the evaluation's concerns that the proposed PBS restriction could potentially be interpreted as broader in scope than the TGA indication, although both were based on the same key clinical evidence, the QUAZAR trial. However, the ESC considered the proposed PBS criteria reflected a defined patient population within the marketing authorisation and that the terminology used in the PBS restriction was applicable to Australian practice (i.e. Patient must have demonstrated complete remission or complete remission with incomplete blood count recovery following standard remission induction chemotherapy with or without consolidation treatment, AND Patient must not be a candidate for, including those who choose not to proceed to, haematopoietic stem cell transplantation).
- 3.5 The ESC noted that the definition of progressive disease (> 15% blasts in the bone marrow) was inconsistent with previous considerations by the PBAC for treatments for AML which have defined progressive disease as > 5% blasts in the marrow not attributable to bone marrow regeneration or another cause (paragraph 2.1, midostaurin Public Summary Document (PSD), July 2018 and paragraph 3.2, gemtuzumab PSD, November 2021). It was also inconsistent with the criteria to determine CR or CRi in the QUAZAR trial (i.e. > 5% blasts in bone marrow). The PSCR revised this criterion to be, 'Patient must not have > 15% blasts in the bone marrow or peripheral blood not attributable to any other cause than AML'. The PSCR added that the approved TGA indication was for continuous therapy, rather than maintenance therapy, and therefore considered that the proposed stopping criteria (i.e. blasts > 15%) was appropriate for continuous treatment. The PSCR claimed that midostaurin and gemtuzumab are not intended for continuous therapy, so it was logical that they had a different stopping rule of > 5% blast count. The PSCR requested that the word 'maintenance' be removed from the proposed PBS indication and treatment phase. The ESC considered that as the QUAZAR trial compared oral azacitidine with BSC as maintenance therapy in patients with AML in complete remission, the removal of the term 'maintenance' from the proposed PBS indication was not reasonable.
- 3.6 The maximum quantity of 21 tablets proposed in the submission was intended to allow for dose escalation in the event of relapse (defined in the approved Product Information as 5% to 15% blasts in the peripheral bone marrow), although it is anticipated that most dispensing's would be for 14 tablets. The ESC considered that allowance of dose escalation was inconsistent with the clinical positioning of oral azacitidine as maintenance therapy (a therapy given post CR/CRi) as the proposed post-relapse dose escalation seeks to continue treatment and reinitiate remission. The ESC noted that data provided in the PSCR relating to dose escalation and noted that although 23.3% of patients in the azacitidine arm returned to remission, so did 11.4% of patients in the BSC arm.

- 3.7 The proposed restriction did not restrict access to oral azacitidine on the basis of cytogenetic risk. The ESC noted that this was inconsistent with the QUAZAR trial which only enrolled patients with intermediate and poor cytogenetic risk. The submission did not provide evidence of efficacy and safety of oral azacitidine in patients with favourable cytogenetic risk.
- 3.8 The proposed PBS restriction is inconsistent with the QUAZAR trial in which patients who had previously achieved CR/CRi following therapy with an hypomethylating agent (HMA) were excluded. The listing of oral azacitidine on the PBS as treatment for patients who have previously received standard intensive remission induction chemotherapy may result in use in patients who have previously received venetoclax plus injectable azacitidine (an HMA).
- 3.9 The ESC and the PBAC considered that the restriction should prevent use in patients post HSCT, as this use was excluded in the key clinical trial.
- 3.10 The approved TGA indication and the proposed PBS restriction specified use of oral azacitidine for adult patients only. The QUAZAR trial included patients of 55 years or older. The PBS restriction for treatment of AML with midostaurin does not restrict treatment by age, although its approved TGA indication is in adults only. The PSCR proposed that the population criteria specifying use in adult patients only could be removed from restriction; the ESC and the PBAC agreed that this was reasonable.
- 3.11 The proposed PBS restrictions do not exclude patients with a FLT3 mutation, which is inconsistent with the clinical algorithm. The QUAZAR trial included approximately 25-30% of patients with an FLT3 mutation. The ESC and the PBAC considered that the restriction should prevent concomitant use of oral azacitidine and midostaurin.
- 3.12 Azacitidine is a Category X drug and an appropriate pregnancy caution should apply to any PBS listing.

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

## **4 Population and disease**

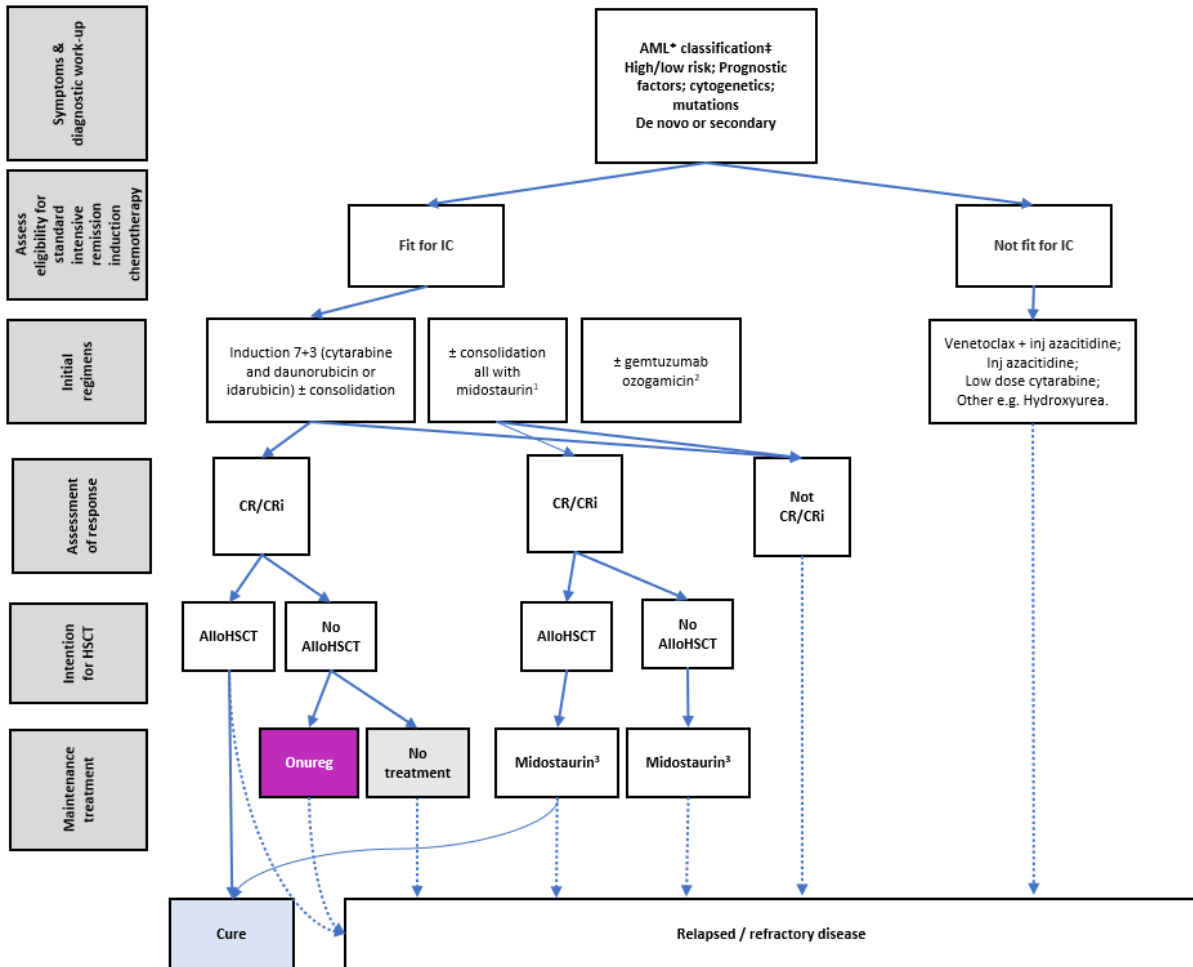
- 4.1 AML is a rare cancer, accounting for 0.8% of all cancers diagnosed despite being the most common acute myeloid malignancy among adults (Sant et al. 2010, Visser et al. 2012, Shallis et al. 2019). AML involves dysfunctional differentiation of myeloblasts and suppression of normal bone marrow haematopoiesis, leading to excessive proliferation of immature blasts and accumulation of leukaemic cells in the bone marrow (Döhner et al. 2015, De Kouchkovsky et al. 2016, Vosberg et al. 2019). AML commonly results from chromosomal abnormalities or single gene mutations.
- 4.2 The signs and symptoms associated with AML are often non-specific and secondary to the development of other conditions. It is diagnosed based on the presence of 20% or more blasts in the bone marrow or peripheral blood in combination with immunohistochemistry, cytogenetics, and molecular analyses (Cheson et al. 2003,

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Arber et al. 2016, Arber et al. 2017, Döhner et al. 2017, Swerdlow et al. 2017, NCCN 2020).

- 4.3 In 2021, the Australian Institute of Health and Welfare (AIHW) ranked AML as the 12th most common cause of death from cancer; ranked 11th and 13th for male and females respectively. The 5-year relative survival of patients in all ages for the 2013-2017 period was 26.3%. Relative survival at 5 years is higher in younger patients (0-19 years: 73.7%; 20-39 years: 72.3%), decreasing to approximately 52% for patients aged 40-59 and becoming worse among older patients 60 years and above (60-79 years: 15.1%; 80+ years: 1.4%) (AIHW Cancer data in Australia 2021; Workbook 'AIHW-CAN-122-CDiA-2021-Book-3b-Cancer-survival-by-age-age-adjusted-estimates').
- 4.4 The submission defined maintenance treatment in AML as treatment given post CR/CRi with the intention of delaying relapse and prolonging survival. The submission supported this with definitions used in the literature for maintenance treatment in AML; for example, the FDA, NCCN guidelines and other randomised clinical trials.
- 4.5 The proposed clinical management algorithm is presented in Figure 1. The submission did not state what sources the proposed clinical management algorithm was based upon; however, it was largely consistent with current practice in Australia and international guidelines, as presented in the submission.

Figure 1: Treatment algorithm indicating positioning of oral azacitidine if made available on the PBS



Source: Figure 7, p34 of the submission.

Abbreviations: AlloHSCT = allogenic haemopoietic stem cell transplant; AML = acute myeloid leukemia; CR = complete remission; CRi = complete remission with incomplete blood count recovery; IC = intensive chemotherapy; PBS = Pharmaceutical Benefit Scheme.

Note: The current standard of no treatment is represented in grey and the positioning of oral azacitidine on the PBS is shown in purple.

<sup>1</sup>The condition must be internal tandem duplication (ITD) or tyrosine kinase domain (TKD) FMS tyrosine kinase 3 (FLT3) mutation positive AML

<sup>2</sup>At the November 2021 PBAC meeting, the PBAC recommended the listing of gemtuzumab ozogamicin, in combination with standard intensive chemotherapy (an anthracycline and cytarabine), for the treatment of patients with previously untreated, de novo CD33-positive AML except acute promyelocytic leukaemia, who have favourable/intermediate/unknown cytogenetic risk (where the unknown risk is due to inconclusive test results). This was PBS-listed on 1 March 2022.

<sup>3</sup>Patient must have demonstrated complete remission after induction and consolidation chemotherapy in combination with midostaurin in order to receive maintenance treatment with midostaurin. The clinical criteria for PBS listed midostaurin for maintenance treatment states that a 'patient must not be undergoing, or have undergone, a stem cell transplant' (paragraph 2.1, midostaurin PSD, July 2018).

4.6 The proposed clinical management algorithm was inconsistent with the evidence presented and the economic model, where a proportion of patients received HSCT post treatment with oral azacitidine (6.3% in the oral azacitidine arm and 13.7% in the BSC arm of QUAZAR). An expert statement provided with the submission estimated the proportion of patients to become fit enough for transplant post treatment to be no more than 15%.

- 4.7 The clinical management algorithm suggested that patients treated with midostaurin as induction therapy will not receive oral azacitidine as maintenance therapy. While it is unlikely that oral azacitidine will displace/replace midostaurin for patients with an FMS-like tyrosine kinase-3 (FLT3) mutation, a proportion of patients who experience severe adverse events with midostaurin induction and/or consolidation may opt for oral azacitidine if it is available for maintenance. A subgroup analysis by FLT3 mutation status demonstrated oral azacitidine provided an improvement in OS compared to BSC regardless of FLT3 mutation status (median time to event for FLT3 mutant patients: 28.2 months (95% CI: NR) versus 9.7 months (95% CI: NR) for oral azacitidine and BSC respectively).
- 4.8 Oral azacitidine is an oral formulation of the HMA azacitidine, a cytidine nucleoside analogue that incorporates into DNA and ribonucleic acid (RNA). Azacitidine exerts its clinical efficacy through reduction of DNA hypermethylation and induction of cytotoxicity in abnormal haematopoietic cells (Garcia-Manero et al. 2016). Best supportive care (BSC) is provided alongside oral azacitidine. BSC includes but is not limited to red blood cell (RBC) and platelet transfusions, antibiotics, antiviral and antifungal therapy, nutritional support and granulocyte colony stimulating factors (G-CSFs).
- 4.9 The recommended dosing schedule of oral azacitidine proposed by the submission was consistent with the oral azacitidine Product Information and the dosing schedule in QUAZAR. Prophylactic concomitant treatment with anti-emetics is recommended 30 minutes prior to each dose of oral azacitidine for the first two treatment cycles, however, anti-emetics can be omitted after 2 cycles if there has been no nausea and vomiting. Complete blood count (CBC) is also recommended prior to initiation of therapy, every other week for the first 2 cycles (56 days), every other week for the next 2 cycles after dose adjustment, and monthly thereafter, prior to the start of subsequent cycles of treatment. Costs of prophylactic anti-emetics and CBCs were included in the economic analysis, but not the estimated financial impact estimates.

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

## **5 Comparator**

- 5.1 The submission nominated placebo or no maintenance therapy as the main comparator. While all AML patients will receive BSC, in addition to active therapy or placebo, the submission referred to the use of BSC in the absence of active therapy as 'placebo'; this will be referred to as 'BSC' hereafter. Patients in the comparator arm of QUAZAR received placebo alongside BSC; the comparator arm of QUAZAR will also be referred to as 'BSC' hereafter. The main argument provided in support of this nomination was that no therapies are currently registered or reimbursed as maintenance therapy for the proposed population. The ESC considered that the choice of comparator was appropriate.

- 5.2 Midostaurin is PBS listed for use in FLT3 mutation positive AML patients as induction/consolidation therapy and as maintenance therapy. While unlikely, there is a possibility that a small proportion of patients with a positive FLT3 mutation who have received midostaurin will receive oral azacitidine as maintenance therapy. Expert opinion provided with the submission noted that for FLT3 mutation positive patients, ‘approximately 5 to 10% of patients may have side-effects related to midostaurin and may access [oral] azacitidine instead’.

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

## **6 Consideration of the evidence**

### ***Sponsor hearing***

- 6.1 There was no hearing for this item.

### ***Consumer comments***

- 6.2 The PBAC noted and welcomed the input from individuals (2) and organisations (2) via the Consumer Comments facility on the PBS website. Comments from individuals and South East Myeloma Support expressed support for the listing of oral azacitidine.
- 6.3 The PBAC noted the advice received from the Leukaemia Foundation. The PBAC specifically noted the advice that the use of oral azacitidine as maintenance therapy for certain patients with AML may improve overall survival and appears to have very acceptable tolerability. The Leukaemia Foundation also noted the unmet need for effective AML maintenance therapies. The PBAC noted that this advice was supportive of the evidence provided in the submission.

### ***Clinical trials***

- 6.4 The submission was based on the QUAZAR trial, a head-to-head, randomised, phase 3 trial comparing oral azacitidine to placebo (BSC) (n=472). The submission presented data from two clinical cut-offs: primary analysis (July 2019 data cut-off) with a median follow-up of 40.2 months, and updated analysis (September 2020 data cut-off) with a median follow-up of 51.7 months.
- 6.5 Results from the September 2020 data cut-off informed the efficacy outcome for OS used in the economic model. Safety and relapse free survival (RFS) outcomes presented in the submission were based on the July 2019 data cut-off, although RFS at the September 2020 data cut-off was also then compiled during the evaluation.
- 6.6 Details of the trials presented in the submission are provided in Table 2.

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**Table 2: Trials and key associated reports presented in the submission**

| <b>Trial ID</b>                      | <b>Protocol title/ Publication title</b>   | <b>Publication citation</b>   |
|--------------------------------------|--|---|
| QUAZAR AML-001 (QUAZAR): NCT01757535 | A Phase 3, Randomized, Double-blind, Placebo-controlled Study to compare efficacy and safety of Oral Azacitidine plus best supportive care versus best supportive care as Maintenance Therapy in subjects with Acute Myeloid Leukemia in complete remission: clinical study report.  | 8 January 2020  |
|                                      | QUAZAR September 2020 Data cut: Survival Analysis Technical Appendix   | 23 March 2021   |
|                                      | Wei, A. H., Döhner, H., Pocock, C., et al. Oral azacitidine maintenance therapy for acute myeloid leukemia in first remission  | NEJM 2020; 383(26), 2526-2537   |
|                                      | Döhner, H., Wei, A.H., Roboz, G., et al. Prognostic Impact of NPM1 and FLT3 Mutations at Diagnosis and Presence of Measurable Residual Disease (MRD) after Intensive Chemotherapy (IC) for Patients with Acute Myeloid Leukemia (AML) in Remission: Outcomes from the QUAZAR AML-001 Trial of Oral Azacitidine (Oral-AZA) Maintenance. | 63rd American Society of Hematology (ASH) Annual Meeting Blood 2021; 138, p.804.                |
|                                      | Ravandi, F., Roboz, G., Wei, A., et al. Hematologic adverse events and management strategies for patients with acute myeloid leukemia (AML) in first remission receiving oral azacitidine (ORAL-AZA) in the phase 3 QUAZAR AML-001 trial.  | European Haematology association (EHA) 2021 meeting HemaSphere 2021; 5(SUPPL 2), 181-182.       |
|                                      | Wei, A.H., Döhner, H., Sayar, H., et al. Long-Term Overall Survival (OS) with Oral Azacitidine (Oral-AZA) in Patients with Acute Myeloid Leukemia (AML) in First Remission after Intensive Chemotherapy (IC): Updated Results from the Phase 3 QUAZAR AML-001 Trial.   | 63rd American Society of Hematology (ASH) Annual Meeting and Exposition Blood 2021; 138, p.871. |

Source: Table 27, pp48-50 of the submission.

Abbreviations: AML = acute myeloid leukemia; AZA = azacitidine; CC-486 = oral azacitidine; IC = intensive chemotherapy; MRD = measurable residual disease; OS = overall survival; RFS = relapse free survival; SUPPL = supplement

- 6.7 The key features of QUAZAR are summarised in Table 3. Overall, the risk of bias in QUAZAR was low. Assessment of disease response (primary and secondary endpoints) were conducted in a blinded manner. The efficacy analysis was based on all patients who were randomised, i.e. the intention-to-treat (ITT) population.
- 6.8 No patients were reported to be lost to follow-up in the oral azacitidine arm and only one patient was lost to follow-up in the BSC arm. Overall, discontinuations were lower for the oral azacitidine arm compared to the BSC arm at the first data cut-off (81% versus 89% respectively). The main reasons for discontinuations were disease relapse, adverse events and withdrawal of consent. The number of patients who discontinued treatment due to adverse events in the oral azacitidine arm was higher compared to the BSC arm (29 versus 11 respectively).

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**Table 3: Key features of the included evidence**

| <b>Trial</b>                       | <b>N</b> | <b>Design</b>      | <b>Risk of bias</b> | <b>Patient population</b>   | <b>Outcomes</b>   | <b>Used in modelled evaluation</b> |
|------------------------------------|----------|--------------------|---------------------|---|---|------------------------------------|
| <b>Oral azacitidine versus BSC</b> |          |                    |                     |   |   |                                    |
| QUAZAR                             | 472      | R, DB, Phase 3, MC | Low                 | Patients aged ≥ 55 years; were newly diagnosed, histologically confirmed de novo AML or AML secondary to prior myelodysplastic disease or CMML; had received induction therapy with intensive chemotherapy ± consolidation therapy; achieved first CR/CRi status within 4 months (± 7 days) prior to randomisation; had an ECOG performance status of 0, 1, 2 or 3. | OS, RFS, safety, HRQoL, time to relapse from CR/CRi, time to discontinuation from treatment | Yes; OS, RFS and safety            |

Source: Table 30, p52, Table 41, pp62-63 of the submission.

Abbreviations: AML = acute myeloid leukaemia; BSC = best supportive care; CMML = chronic myelomonocytic leukaemia; CR = complete response; CRi = complete response with incomplete blood count recovery DB = double blind; ECOG = Eastern Cooperative Oncology Group; HRQoL = health related quality of life; MC = multi-centre; OS = overall survival; RFS = relapse free survival; R = randomised.

- 6.9 The baseline characteristics of the treatment groups were similar, except for measurable residual disease (MRD) status, where 43% of patients in the oral azacitidine arm were positive compared to 50% in the BSC arm. The submission acknowledged that MRD has negative prognostic value with MRD positive patients reported as having a significantly higher relapse rate (Buccisano et al. 2010) and presented relevant subgroup analyses. Patients who were MRD positive were less likely to survive compared to those who were MRD negative (median time to event in the BSC arm: MRD positive = 10.4 months versus MRD negative = 24.3 months). This biased the results against the BSC arm.
- 6.10 A higher proportion of patients randomised to the oral azacitidine arm reported dose adjustments attributable to adverse events. The submission noted this as reasonable given the use of an active anti-cancer drug compared with patients receiving BSC. In addition, the submission stated the prolonged time to the first dose reduction due to an adverse event in the oral azacitidine arm (mean 179 days) is suggestive of oral azacitidine being reasonably well tolerated over a prolonged treatment period. This was reasonable.
- 6.11 Health related quality of life (HRQoL) data were obtained in QUAZAR using the EQ-5D-3L instrument and the FACIT-Fatigue scale, a subscale of the FACIT-F instrument. The FACIT-Fatigue scale is a 13-question disease-specific scale with scores ranging from 0 to 52, with higher scores indicating less fatigue. HRQoL data were collected on Day 1 of each 28-day treatment cycle and upon treatment discontinuation.
- 6.12 The submission proposed minimum clinically important differences for HRQoL based on published literature. For the FACIT-Fatigue Scale, a change from baseline of ≥ 3 points was used to define clinically meaningful improvement and worsening at the individual level (Cella et al. 2002). For the EQ-5D-3L health utility index, a 0.08 point and 0.10 point or greater changes from baseline were used to define clinically

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meaningful improvement or worsening respectively (Pickard et al. 2007, Kvam et al. 2011).

**Comparative effectiveness**

6.13 The results from the primary and updated analysis of OS are presented in Table 4 and Figure 2. There was a statistically significant improvement in OS for the oral azacitidine arm at both data cut-off dates.

**Table 4: Results of overall survival in QUAZAR trial (ITT population)**

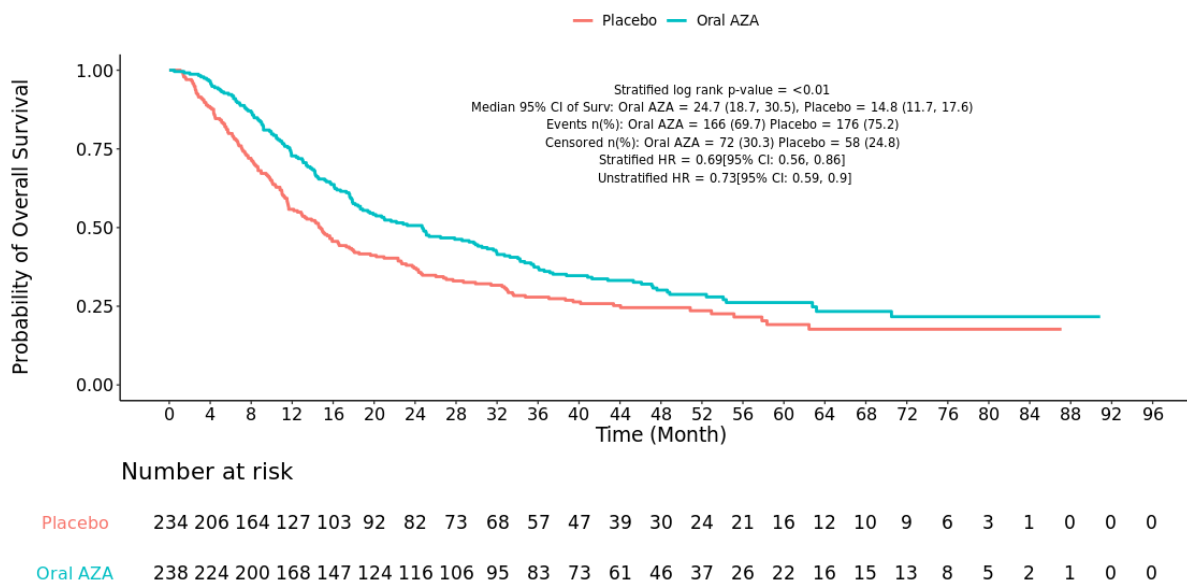
|  | Oral azacitidine |                               | BSC           |                               | Difference in median | P value (log rank test) | Hazard ratio (95% CI)    |
|--|------------------|-------------------------------|---------------|-------------------------------|----------------------|-------------------------|--------------------------|
|  | n/N (%)          | Median time to event (95% CI) | n/N (%)       | Median time to event (95% CI) |                      |                         |                          |
| <b>Primary analysis (median follow-up 40.2 months)</b> | 158/238 (66%)    | 24.7 months (18.7, 30.5)      | 171/234 (73%) | 14.8 months (11.7, 17.6)      | 9.9                  | <0.001                  | <b>0.69 (0.55, 0.86)</b> |
| <b>Updated analysis (median follow-up 51.7 months)</b> | 165/238 (69%)    | 24.7 months (18.7, 30.5)      | 176/234 (75%) | 14.8 months (11.7, 17.6)      | 9.9                  | 0.0008                  | <b>0.69 (0.56, 0.86)</b> |

Source: Table 42, p67 of the submission; Figure 1, p14 of the QUAZAR September 2020 Data-cut Survival Analysis Technical Appendix Docx.

Abbreviations: BSC = best supportive care; CI = confidence interval; ITT = intention to treat; n = number of participants reporting data; N = total participants in group

Bold indicate statistically significant.

**Figure 2: Kaplan–Meier analysis of overall survival in QUAZAR trial (ITT population); September 2020 data cut-off**



Source: Figure 1, p13 of 'QUAZAR September 2020 Datacut Survival Analysis Technical Appendix' of the submission

Abbreviations: AZA = azacitidine; CI = confidence interval; HR = hazard ratio; ITT = intention to treat

Note: Placebo = BSC

6.14 The submission provided the results of RFS for only the primary analysis data cut-off, July 2019; Table 5 and Figure 3. Results of RFS for the updated data cut-off, September 2020 were compiled during the evaluation in Table 5.

Table 5: Duration of relapse-free survival reported in the QUAZAR trial (ITT population)

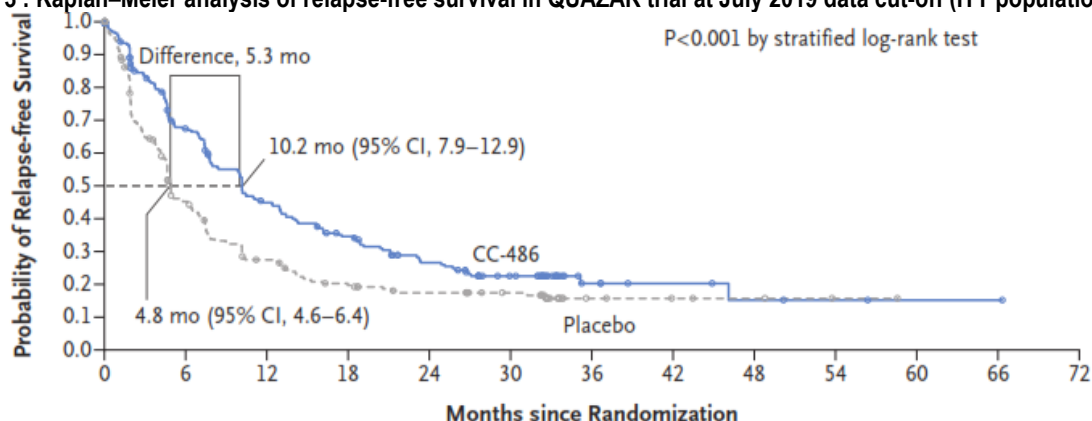
|  | Oral azacitidine |                               | BSC           |                               | Difference in median | P value (log rank test) | Hazard ratio (95% CI)    |
|--|------------------|-------------------------------|---------------|-------------------------------|----------------------|-------------------------|--------------------------|
|  | n/N (%)          | Median time to event (95% CI) | n/N (%)       | Median time to event (95% CI) |                      |                         |                          |
| <b>Primary analysis (median follow-up 40.2 months)</b> | 164/238 (69%)    | 10.2 months (7.9, 12.9)       | 181/234 (77%) | 4.8 months (4.6, 6.4)         | 5.3                  | 0.0001                  | <b>0.65 (0.52, 0.81)</b> |
| <b>Updated analysis (median follow-up 51.7 months)</b> | 165/238 (69%)    | 10.2 months (7.9, 12.9)       | 182/234 (78%) | 4.8 months (4.6, 6.4)         | 5.3                  | <0.01                   | <b>0.65 (0.52, 0.80)</b> |

Source: Table 45, p71 of the submission and Figure 20, p28 of 'QUAZAR September 2020 Datacut Survival Analysis Technical Appendix' of the submission

Abbreviations: BSC = best supportive care; CI = confidence interval; ITT = intention to treat; n = number of participants reporting data; N = total participants in group

Bold indicate statistically significant.

Figure 3 : Kaplan–Meier analysis of relapse-free survival in QUAZAR trial at July 2019 data cut-off (ITT population)



| No. at Risk |     |     |    |    |    |    |   |   |   |   |   |   |   |
|-------------|-----|-----|----|----|----|----|---|---|---|---|---|---|---|
| CC-486      | 238 | 143 | 92 | 68 | 47 | 30 | 8 | 5 | 3 | 2 | 1 | 1 | 0 |
| Placebo     | 234 | 96  | 55 | 37 | 29 | 23 | 6 | 4 | 3 | 1 | 0 |   |   |

Source: Figure 14, p71 of the submission

Abbreviations: CC-486 = oral azacitidine arm; CI = confidence interval; ITT = intention to treat

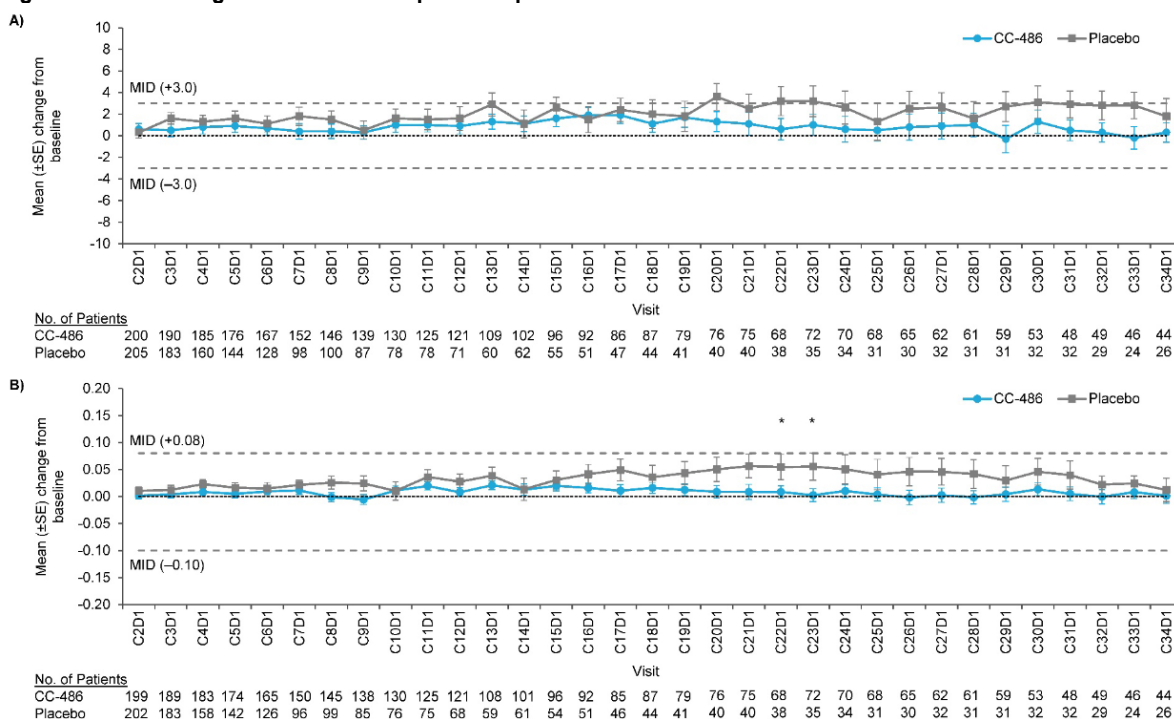
Note: Placebo = BSC

6.15 The HRQoL evaluable population comprised 225/238 (95%) patients in the oral azacitidine arm and 219/234 (94%) in the BSC arm. While questionnaire compliance rates were high, smaller numbers of patients remained available to provide HRQoL assessments over time; < 25 and < 10 patients at Cycle 50 for the oral azacitidine arm and the BSC arm respectively. The decline in the number of patients was a result of patients discontinuing treatment (all causes) at any given point in time. Accordingly, observed HRQoL values for those latter cycles will be more heavily influenced by 'better' performing patients.

6.16 The plots of the mean change from baseline in FACIT-Fatigue Score and EQ-5D-3L health utility value are presented in Figure 4. The submission noted data were reported up to Cycle 34, the last cycle with ≥ 25 patients in both treatment arms, thus, considered appropriate to undertake a meaningful comparative assessment of HRQoL.

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Figure 4: Mean change from baseline in patient reported outcome in QUAZAR



Source: Figure 15, p75 of the submission

Abbreviations: CC-486=oral azacitidine; CXD1=Cycle number, Day 1; MID=minimally important difference

Note: A: FACIT-Fatigue Score; B: EQ-5D-3L health utility score

6.17 In terms of HRQoL, the submission claimed oral azacitidine was noninferior to BSC based on the absence of a statistically significant or clinically meaningful difference (as outlined in paragraph 6.9 above) between the two treatment arms for both the FACIT-Fatigue scale and the EQ-5D-3L instruments. There were no clinically meaningful or statistically significant differences between oral azacitidine and BSC in HRQoL in terms of change from baseline at the end points (Cycle 34). However, it was difficult to conclude noninferiority given (i) HRQoL change from baseline appeared to be superior in the BSC arm compared to the oral azacitidine arm at various time points throughout the follow-up period (suggesting a difference in the area-under the curve), and (ii) the number of patients remaining available to make HRQoL assessments over time decreased.

**Subgroup analyses**

6.18 Although not seeking the listing of oral azacitidine for a particular subgroup of patients from the QUAZAR trial, the submission presented subgroup analyses for OS to explore the treatment effect of oral azacitidine in some patient subgroups. The submission noted that the analyses were exploratory in nature as QUAZAR was not powered to test for statistical significance of any difference in OS reported in subgroups of the ITT

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population. In addition, the subgroups were not prespecified. The submission did not present subgroup analyses based on RFS.

6.19 The subgroup analyses explored by the submission were with respect to:

- Age at time of induction therapy (55-64 years, ≥ 65 years)
- Prior history of MDS (yes/no)
- Whether consolidation therapy was administered (yes/no)
- Cytogenetic risk category at time of induction therapy (intermediate risk, poor risk)
- FLT3 mutation status (mutant/wild-type)
- MRD status (positive/negative)

6.20 The results from these analyses favoured oral azacitidine compared to BSC (i.e. OS was greater in the oral azacitidine arm) in all patient subgroups except patients who received 3 cycles of consolidation after induction chemotherapy. According to the detailed subgroup analysis presented by the TGA Delegate (see Table 6 below), there was a trend towards less treatment effect in patients who had undergone more cycles of consolidation prior to treatment. The hazard ratio (HR) for OS ranged between 0.54 (95% CI: 0.33, 0.87) for patients who had not undergone prior consolidation (n=94) to 0.99 (95% CI: 0.23, 4.25) for those who had received three cycles of consolidation (n=19). The ESC noted the small patient numbers in the 3 cycles of consolidation group. The ESC considered that standard practice in Australia is 2 cycles of consolidation.

**Table 6: Subgroup analysis of overall survival by number of consolidation cycles**

|                            | No consolidation  |                    | 1 cycle of consolidation |                     | 2 cycles of consolidation |                    | 3 cycles of consolidation |                   |
|----------------------------|-------------------|--------------------|--------------------------|---------------------|---------------------------|--------------------|---------------------------|-------------------|
|                            | PBO<br>N = 42     | Oral AZA<br>N = 52 | PBO<br>N = 102           | Oral AZA<br>N = 110 | PBO<br>N = 77             | Oral AZA<br>N = 70 | PBO<br>N = 13             | Oral AZA<br>N = 6 |
| Patients with event, n (%) | 33 (79%)          | 36 (69%)           | 80 (78%)                 | 79 (72%)            | 52 (68%)                  | 39 (56%)           | 6 (46%)                   | 4 (67%)           |
| Patients censored, n (%)   | 9 (21%)           | 16 (31%)           | 22 (22%)                 | 31 (28%)            | 25 (32%)                  | 31 (44%)           | 7 (54%)                   | 2 (33%)           |
| HR (95% CI) <sup>a</sup>   | 0.54 (0.33, 0.87) |                    | 0.73 (0.53, 1.00)        |                     | 0.68 (0.44, 1.04)         |                    | 0.99 (0.23, 4.25)         |                   |
| HR (95% CI) <sup>b</sup>   | 0.55 (0.34, 0.89) |                    | 0.75 (0.55, 1.02)        |                     | 0.69 (0.45, 1.04)         |                    | 1.37 (0.37, 5.02)         |                   |

Source: Table 36, p100 of the USA FDA Multi-discipline review, cited in the TGA Delegate's Overview, Table 6, p10

Abbreviations: AZA = azacitidine; HR = hazard ratio; PBO = placebo

a Estimated with Cox proportional hazard model and log-rank test stratified by age at time of induction therapy (55-64 versus ≥ 65 years), cytogenetic risk category at time of induction therapy (intermediate versus poor risk) and received consolidation therapy following induction therapy (yes versus no)

b Estimated with unstratified Cox proportional hazard model and log-rank test

6.21 The submission argued the results from the subgroup analyses of OS do not support restricting the use of oral azacitidine in any specific subgroup(s) of patients enrolled in the QUAZAR trial.

## Comparative harms

### Treatment emergent adverse events

- 6.22 The submission presented a summary of treatment emergent adverse events (TEAEs) in the safety population (defined as all randomised patients who received at least 1 dose of study treatment) based on the primary analysis (July 2019 data cut-off), Table 7.
- 6.23 The submission argued that the proportions of patients who experienced TEAEs  $\geq$  Grade 3 in both treatment arms suggested that concomitant BSC treatments may have contributed to the rate reported in the oral azacitidine arm. While the rate of TEAEs  $\geq$  Grade 3 was high in both the oral azacitidine and BSC arm, a higher rate was observed in the oral azacitidine arm. A higher rate of TEAEs resulting in treatment discontinuation was also observed in the oral azacitidine arm compared to the BSC arm.

**Table 7: Summary of TEAEs in QUAZAR (safety population)**

|   | Oral azacitidine.<br>n/N (%) | BSC.<br>n/N (%)             |
|---|------------------------------|-----------------------------|
| TEAE (all-causality)  | 231/236 (98%)                | 225 <sup>a</sup> /233 (97%) |
| TEAE $\geq$ Grade 3 (all-causality)                         | 169/236 (72%)                | 147/233 (63%)               |
| TEAE resulting in treatment discontinuation (all-causality) | 31/236 (13%)                 | 10/233 (4%)                 |
| TEAE leading to death                                       | 9/236 (4%)                   | 4/233 (2%)                  |

Source: Table 50, p76 of the submission.

Abbreviations: BSC = best supportive care; n = number of participants reporting data; N = total participants in group; TEAEs = treatment emergent adverse events.

<sup>a</sup> Incorrectly reported as 255 in the submission.

### Individual frequently reported TEAEs

- 6.24 Frequently reported TEAEs experienced by  $\geq$  10% of QUAZAR patients are presented in Table 8. In the oral azacitidine arm, the five most frequently reported TEAEs (any grade) were nausea (65%), vomiting (60%), diarrhoea (50%), neutropenia (44%) and constipation (39%). In the BSC arm, they were thrombocytopenia (27%), neutropenia (26%), nausea (24%), constipation (24%) and diarrhoea (21%).
- 6.25 While the above mentioned TEAEs were frequently reported in both the oral azacitidine and BSC arms, a higher rate was observed in the oral azacitidine arm. A higher rate of fatigue, asthenia, abdominal pain, decreased appetite and pain in extremity was also observed for the oral azacitidine arm.

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Table 8: Frequently reported adverse events in the QUAZAR trial (safety population)

|                                   | Any Grade               |            | Grade 3-4               |            |
|-----------------------------------|-------------------------|------------|-------------------------|------------|
|                                   | Oral azacitidine, n (%) | BSC, n (%) | Oral azacitidine, n (%) | BSC, n (%) |
| <b>N</b>                          | <b>236</b>              | <b>233</b> | <b>236</b>              | <b>233</b> |
| Any adverse event                 | 231 (98%)               | 225 (88%)  | 169 (47%)               | 147 (38%)  |
| Nausea                            | 153 (65%)               | 55 (24%)   | 6 (3%)                  | 1 (<1%)    |
| Vomiting                          | 141 (60%)               | 23 (10%)   | 7 (3%)                  | 0          |
| Diarrhoea                         | 119 (50%)               | 50 (21%)   | 12 (5%)                 | 3 (1%)     |
| Neutropenia                       | 105 (44%)               | 61 (26%)   | 97 (41%)                | 55 (24%)   |
| Constipation                      | 91 (39%)                | 56 (24%)   | 3 (1%)                  | 0          |
| Thrombocytopenia                  | 79 (33%)                | 63 (27%)   | 53 (22%)                | 50 (21%)   |
| Fatigue                           | 70 (30%)                | 45 (19%)   | 7 (3%)                  | 2 (1%)     |
| Anaemia                           | 48 (20%)                | 42 (18%)   | 33 (14%)                | 30 (13%)   |
| Asthenia                          | 44 (19%)                | 13 (6%)    | 2 (1%)                  | 1 (<1%)    |
| Pyrexia                           | 36 (15%)                | 44 (19%)   | 4 (2%)                  | 1 (<1%)    |
| Arthralgia                        | 32 (14%)                | 24 (10%)   | 2 (1%)                  | 1 (<1%)    |
| Abdominal pain                    | 31 (13%)                | 16 (7%)    | 2 (1%)                  | 0          |
| Upper respiratory tract infection | 31 (13%)                | 32 (14%)   | 1 (<1%)                 | 0          |
| Decreased appetite                | 30 (13%)                | 15 (6%)    | 2 (1%)                  | 2 (1%)     |
| Cough                             | 29 (12%)                | 39 (17%)   | 0                       | 0          |
| Febrile neutropenia               | 28 (12%)                | 18 (8%)    | 27 (11%)                | 18 (8%)    |
| Back pain                         | 28 (12%)                | 23 (10%)   | 3 (1%)                  | 2 (1%)     |
| Leukopenia                        | 25 (11%)                | 19 (8%)    | 18 (8%)                 | 14 (6%)    |
| Pain in extremity                 | 25 (11%)                | 12 (5%)    | 1 (<1%)                 | 0          |
| Dizziness                         | 25 (11%)                | 21 (9%)    | 0                       | 0          |
| Headache                          | 23 (10%)                | 26 (11%)   | 0                       | 1 (<1%)    |
| Peripheral oedema                 | 21 (9%)                 | 24 (10%)   | 0                       | 1 (<1%)    |

Source: Table 51, p78 of the submission.

Abbreviations: BSC = best supportive care; n = number of participants reporting data; N = total participants in group

Note: *Italicised was corrected during the evaluation; incorrectly reported by the submission.*

## Haematological TEAEs

6.26 A higher rate of haematological adverse events was observed in the oral azacitidine arm compared to the BSC arm.

Table 9: Haematological adverse events reported in the QUAZAR trial (safety population)

|                                | Oral azacitidine, n/N (%) | BSC, n/N (%)  |
|--------------------------------|---------------------------|---------------|
| Any haematologic adverse event | 155/236 (66%)             | 110/233 (47%) |
| Neutropenia                    | 105/236 (44%)             | 61/233 (26%)  |
| Thrombocytopenia               | 79/236 (33%)              | 63/233 (27%)  |
| Anaemia                        | 48/236 (20%)              | 42/233 (18%)  |

Source: Table 52, p79 of the submission.

Abbreviations: BSC = best supportive care; n = number of participants reporting data; N = total participants in group.

## Benefits/harms

6.27 A summary of comparative benefits and harms for oral azacitidine compared to BSC is presented in Table 10.

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**Table 10: Summary of comparative benefits and harms for oral azacitidine compared with BSC (ITT population, Primary analysis (July 2019 data cut-off))**

| <b>Benefits</b>   |                              |                   |                            |   |            |           |
|---|------------------------------|-------------------|----------------------------|---|------------|-----------|
|   | <b>Oral azacitidine</b>      | <b>BSC</b>        | <b>Absolute difference</b> | <b>HR (95% CI) (p value)</b>            |            |           |
| <b>Relapse-free survival (median duration of follow up 40.2 months)</b> |                              |                   |                            |   |            |           |
| Relapsed, n/N (%)   | 164/238 (69%)                | 181/234 (77%)     | -                          | <b>0.65 (0.52, 0.81)</b><br>p = 0.0001  |            |           |
| Median RFS, months (95% CI)   | 10.2 (7.9, 12.9)             | 4.8 (4.6, 6.4)    | 5.3 months                 |   |            |           |
| % not relapsed at 1 year (95% CI)                                       | 45% (38%, 51%)               | 27% (22%, 34%)    | 18%                        |   |            |           |
| % not relapsed at 2 years (95% CI)                                      | 27% (21%, 33%)               | 17% (13%, 23%)    | 10%                        |   |            |           |
| <b>Overall survival (median duration of follow up 40.2 months)</b>      |                              |                   |                            |   |            |           |
| Deaths, n/N (%)   | 158/238 (66%)                | 171/234 (73%)     |                            | <b>0.69 (0.55, 0.86)</b><br>p = < 0.001 |            |           |
| Median OS, months (95% CI)  | 24.7 (18.7, 30.5)            | 14.8 (11.7, 17.6) | 9.9 months                 |   |            |           |
| % alive at 1 year (95% CI)  | 73% (67%, 78%)               | 56% (49%, 62%)    | 17%                        |   |            |           |
| % alive at 2 years (95% CI)   | 51% (44%, 57%)               | 37% (31%, 43%)    | 14%                        |   |            |           |
| <b>Harms</b>  |                              |                   |                            |   |            |           |
|   | <b>Oral azacitidine, n/N</b> | <b>BSC, n/N</b>   | <b>RR</b>                  | <b>Event rate/100 patients</b>          |            | <b>RD</b> |
|   |                              |                   |                            | <b>Oral azacitidine</b>                 | <b>BSC</b> |           |
| TEAE (all causality)  | 231/236                      | 225/233           | 1.01                       | 98                                      | 97         | 0.01      |
| TEAE ≥ Grade 3 (all-causality)  | 169/236                      | 147/233           | 1.14                       | 72                                      | 63         | 0.09      |
| TEAE resulting in treatment discontinuation (all-causality)             | 31/236                       | 10/233            | 3.06                       | 13                                      | 4          | 0.09      |
| TEAE leading to death   | 9/236                        | 4/233             | 2.22                       | 4                                       | 2          | 0.02      |
| Any haematologic adverse event  | 155/236                      | 110/233           | 1.39                       | 66                                      | 47         | 0.19      |

Source: Table 42, p67; Table 45, p71; Table 52, p79 of the submission; Table 15, p93 and Table 19, p103 of QUAZAR Clinical Study Report of the submission.

Abbreviations: BSC = best supportive care; CI = confidence interval; HR = hazard ratio; n = number of participants reporting data; N = total participants in group; NR = not reported; OS = overall survival; RD = risk difference; RFS = relapse-free survival; RR = risk ratio; TEAEs = treatment emergent adverse events

Bold indicates statistically significant.

6.28 On the basis of the direct evidence presented in QUAZAR at the primary analysis (July 2019 data cut-off), for every 100 patients treated with oral azacitidine in comparison with BSC:

- Approximately 10 fewer patients would have relapsed at 2 years.
- Approximately 14 fewer patients would have died at 2 years.
- Approximately 19 additional patients would experience a haematologic adverse events over a median duration of treatment of 40.2 months.

**Clinical claim**

6.29 On the basis of the direct evidence from the QUAZAR trial, the submission claimed that oral azacitidine was superior in terms of effectiveness and inferior in terms of safety compared with BSC. The clinical claim of effectiveness was based on OS, and the clinical claim of safety was based on comparison of all TEAEs, frequently reported TEAEs (any Grade and Grade 3-4) and haematologic adverse events.

6.30 The ESC considered that the clinical claims were supported by the results presented in the submission, noting that:

- In terms of clinical effectiveness there was a statistically significant improvement in OS for the oral azacitidine arm compared to the BSC arm (HR = 0.69; 95% CI: 0.56, 0.86 at 51.7 months median follow-up).
- In terms of safety, TEAEs resulting in treatment discontinuation, a considerable number of individual TEAEs (any Grade: nausea, vomiting, diarrhoea, neutropenia, constipation, fatigue, asthenia, abdominal pain, decreased appetite and pain in extremity; Grade 3-4: neutropenia) and all haematologic TEAEs were reported more frequently in the oral azacitidine arm than in the BSC arm.

6.31 The PBAC considered that the claim that oral azacitidine was superior in terms of comparative effectiveness and inferior in terms of comparative safety compared to BSC was reasonable.

### ***Economic analysis***

6.32 The economic evaluation presented was a cost-utility analysis. Health benefits were reported as RFS years gained, life years (LYs) gained, and quality adjusted life years (QALYs) gained. The key aspects of the economic evaluation are summarised in Table 11.

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

| <b>Component</b>                 | <b>Summary</b>  |
|----------------------------------|---|
| Treatments                       | Oral azacitidine versus BSC   |
| Time horizon                     | 20 years in the model base case versus 4.3 years (51.7 months) median follow-up at September 2020 data cut-off in QUAZAR. This may be optimistic, given the starting age in the model was 68 years and patients were ineligible for HSCT.   |
| Outcomes                         | Quality adjusted life years, life years, relapse-free life years  |
| Methods used to generate results | Partitioned survival approach, incorporating a cohort expected value analysis.  |
| Health states                    | Relapse free (on treatment and off treatment substates), relapse, death.  |
| Cycle length                     | 28 days   |
| Allocation to health states      | Determined by RFS (July 2019 data cut-off) and OS (September 2020 data cut-off) Kaplan–Meier curves from QUAZAR.<br>The on-treatment phase for oral azacitidine within the relapse-free health state was based on the censored mean duration of treatment (18.1 months) from QUAZAR. The submission presented a sensitivity analysis using time on treatment Kaplan–Meier data from the QUAZAR.   |
| Extrapolation method             | Kaplan–Meier estimates of time to relapse and time to death from QUAZAR were applied up to the point that the submission considered the data had excessive censoring and was unreliable. The base case extrapolated functions were based on parametric models fitted to each treatment arm and were based on visual inspection and goodness of fit (AIC and BIC).<br><br>The functional forms applied in base case were:<br>OS: log-normal<br>RFS: log-logistic<br>The forms applied in the base case were second-best selected based on the AIC and BIC parameters. The best fit functions (based on AIC and BIC) were generalised gamma (OS) and Gompertz (RFS); however, visual inspection suggested clinical implausibility. Based on visual inspection the selection of the parametric models was appropriate.<br><br>The extrapolation point for OS was 69 cycles (63 months), at which 16/238 (6.7%) of patients in the oral azacitidine arm and 12/234 (5.1%) of patients in the BSC arm remained at risk. The point of extrapolation chosen by the submission may be unreliable due significant censoring occurring prior to this time point. The model is sensitive to the point of extrapolation for OS.<br><br>RFS extrapolation began at 35 cycles (32 months), at which 30/238 (12.6%) of patients in the oral azacitidine arm and 23/234 (9.8%) of patients in the BSC arm remained at risk. The point extrapolation for the RFS curve was reasonable. |
| Health related quality of life   | Relapse free (on-treatment and off treatment): 0.83<br>Based on QUAZAR EQ-5D data, equal for both arms. The mean utility value was based on a repeated measures mixed effect model that accounted for reduction in utility due to adverse events. Treatment specific utility values of 0.846 for patients in the azacitidine arm and 0.853 for patients in the BSC arm based on the QUAZAR trial were applied in the revised model presented in the pre-PBAC response.<br><br>Relapse: 0.51<br>Based on published literature (Joshi et al., 2019).<br><br>The evaluation and the ESC considered that the application of the same utility value for both treatment arms may not be reasonable given the difficulties in concluding that HRQoL is noninferior in the oral azacitidine arm compared with the BSC arm. In addition, given patients in the oral azacitidine arm experienced more severe AEs than patients in the BSC arm the application of a single utility value for both treatment arms may overestimate the utility applied in the oral azacitidine arm.   |

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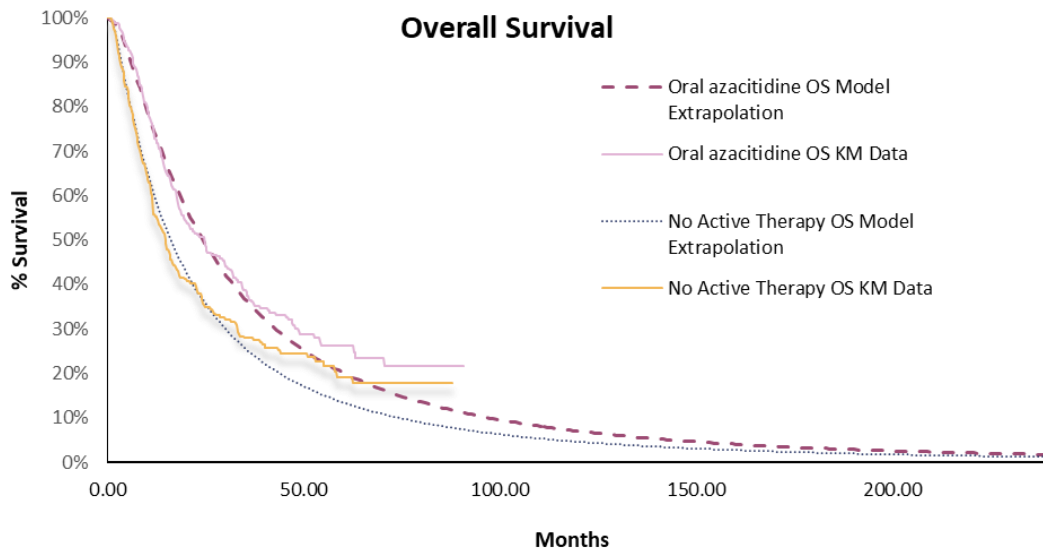
| <b>Component</b>     | <b>Summary</b>  |
|----------------------|---|
| Adverse events       | The model included and applied the costs of treatment for ≥ Grade 3 diarrhoea/vomiting/nausea, ≥ Grade 3 neutropenia, anaemia/thrombocytopenia, ≥ Grade 3 febrile neutropenia and ≥ Grade 3 fatigue for both the oral azacitidine and the BSC arms. This was reasonable.  |
| Stem cell transplant | The proportion of patients receiving a HSCT was included in the model based on the HSCT rates for each arm reported in QUAZAR: 6.3% for oral azacitidine, 13.7% for BSC. The cost was included as a single cost at the start of treatment. Additionally, the submission applied a cost of HSCT (\$21,087) based on the cost of autologous HSCT in the base case. AML patients will undergo allogenic HSCT only at a cost of \$123,956. The correct cost of \$123,956 was applied in the revised model presented in the pre-PBAC response. |

Source: Compiled during evaluation.

Abbreviations: AIC = Akaike Information Criteria; BIC = Bayesian Information Criteria; BSC = best supportive care; EQ-5D =self-assessed, health related, quality of life questionnaire; HSCT = haematopoietic stem cell transplantation.; RFS = relapse free survival; OS = overall survival; QALY = quality adjusted life year.

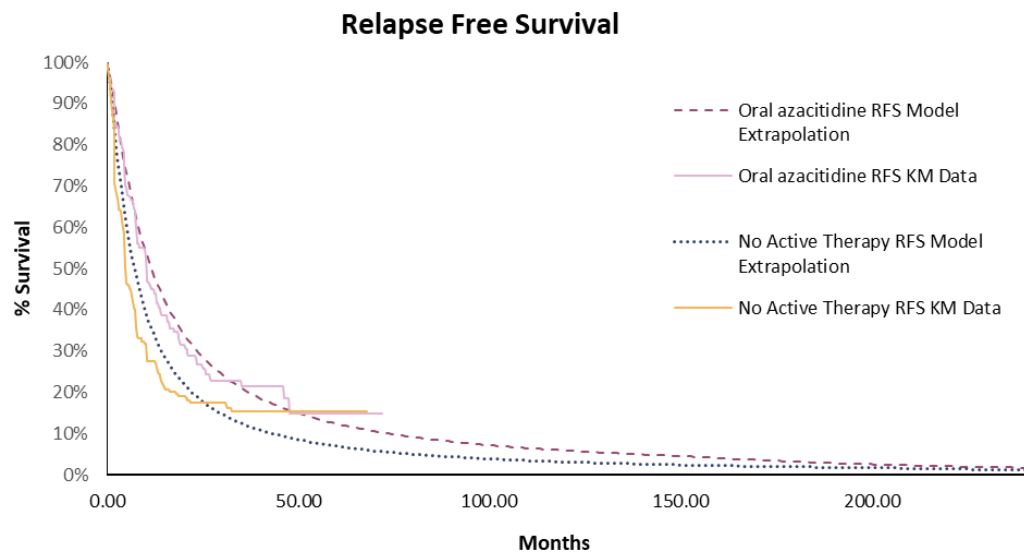
- 6.33 The submission applied a log-normal extrapolation to the Kaplan–Meier data for OS from 69 cycles (63 months), at which point 6.7% of patients in the oral azacitidine arm and 5.1% of patients in the BSC arm remained at risk. The point of extrapolation for OS chosen by the submission may be unreliable due significant censoring occurring prior to this time point. Applying the extrapolated OS curve from the median follow-up point (51.7 months (approximately 55 cycles) at which point 37/238 (16%) of patients in oral azacitidine arm and 24/234 (10%) of patients in BSC arm remained at risk) had a moderate impact on the incremental cost-effectiveness ratio (ICER). The PSCR stated that as the use of the median duration of follow-up as the point of extrapolation did not incorporate 11.3 months of observed time-to-event data it was therefore considered a less robust assessment of the cost-effectiveness of oral azacitidine compared to the base case presented in the submission. The ESC noted that although the choice of the log-normal extrapolation function was reasonable, the point of extrapolation was unreliable due to the significant censoring. The ESC considered that it would be more appropriate to extrapolate the OS curves from an earlier time point, such as the median follow-up point as suggested in the evaluation. The pre-PBAC response reiterated that the approach used in the submission (extrapolation from 69 cycles) was appropriate.
- 6.34 The extrapolation functions for OS and RFS used in the base case analysis are presented in Figure 5 and Figure 6, respectively.

Figure 5: The log-normal extrapolation function was applied to OS in both arms



Source: Excel spreadsheet 'Onureg CUA Workbook.xls', sheet 'Efficacy'  
 Abbreviations: KM = Kaplan–Meier OS = overall survival.

Figure 6: The log-logistic extrapolation function was applied to RFS in both arms



Source: Excel spreadsheet 'Onureg CUA Workbook.xls', sheet 'Efficacy'  
 Abbreviations: KM = Kaplan–Meier; RFS = relapse free survival.

6.35 The submission based the treatment duration for oral azacitidine in the model on the QUAZAR censored mean treatment duration of 18.1 months (standard deviation: 17.2), arguing that application of the censored mean value was 'appropriate for decision-making as it reflects the cost of treatment for the 'average' patient and is less prone to confounding by outlying patients who receive a very short or very long duration of treatment in the QUAZAR trial'. The model assumed that all patients in the

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RFS health state up to 18.1 months received treatment, whilst beyond 18.1 months, no patients received treatment. The ESC noted that this underestimated the cost of oral azacitidine treatment per patient. Applying Kaplan–Meier time on treatment data from QUAZAR (oral azacitidine 74 months (80 cycles) and BSC 68 months (74 cycles)) had a high impact on the ICER. Although there was no extrapolation applied to time on treatment, only a small number of patients remained on treatment at the last available data point. The PBAC noted that there was an error in the calculation of azacitidine costs in the model and although the submission stated that azacitidine patients received an average of 18.1 months of treatment, they actually received an average of 15 months. This was because the calculations also took into account the proportion of patients who were relapse free in each cycle and thus not every patient was treated during the 18.1 months (refer to the ‘RFS adjustment factor’ in Table 16). When using the Kaplan–Meier time on treatment data, patients received an average of 18 months treatment.

- 6.36 The ESC considered that the time horizon of 20 years for a patient commencing treatment at 68 years and who is ineligible for HSCT was reasonable.
- 6.37 The proportion of patients receiving HSCT in the model was based on the HSCT rates for each arm reported in QUAZAR: 6.3% for oral azacitidine, 13.7% for BSC. There is a possibility the lower rate of HSCT in the oral azacitidine arm relative to BSC would not be observed in clinical practice given that the improved relapse status with oral azacitidine may result in more patients undergoing HSCT. The PSCR stated that it was clinically plausible that there may be a reduced rate of HSCT in the azacitidine arm relative to the BSC arm as oral azacitidine is an active anti-cancer treatment used with the intent of maintaining patients in remission following induction therapy with or without consolidation. The ESC considered that this was reasonable. The submission applied a cost of HSCT of \$21,087 based on the cost of autologous HSCT (based on AR-DRG R06). However, AML patients will undergo allogenic HSCTs only. These are more expensive than autologous transplants (weighted cost of AR-DRGs R05A and R05B was \$123,956). Applying the cost of allogenic HSCT (\$123,956) had a significant impact on the ICER in favour of oral azacitidine. Applying the cost of allogenic HSCT (\$123,956) and a similar rate of transplant in both arms (13.7% in the BSC and oral azacitidine arms) had a minor impact on the ICER in favour of oral azacitidine (see Table 15) as the cost of HSCT is modelled as a once off, up-front cost. This was corrected in the revised model presented in the pre-PBAC response.
- 6.38 The ESC noted that the application of the same utility value (0.83) for both treatment arms may not have been reasonable given the difficulties in concluding that HRQoL was noninferior in the oral azacitidine arm compared with the BSC arm. In addition, given patients in the oral azacitidine arm experienced more severe AEs than patients in the BSC arm, the application of a single utility value for both treatment arms may have overestimated the utility applied in the oral azacitidine arm. The economic model did not allow for testing of different utility values in each arm. The pre-PBAC response

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revised the model to allow the incorporation of treatment specific utility values that were based on the QUAZAR trial data for the relapse free health state. A value of 0.846 was applied to the azacitidine arm and 0.853 to the BSC arm.

6.39 A summary of the key drivers of the model is presented in Table 12.

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

| Description               | Method/Value   | Impact<br>Base case: \$ <sup>1</sup> /QALY gained   |
|---------------------------|--|---|
| Duration of treatment     | The submission stated that it applied the censored mean duration of treatment 18.1 months.   | High, favours oral azacitidine<br>Use of ToT KM data increased the ICER to \$ <sup>1</sup> /QALY gained.  |
| Cost of HSCT              | Cost of autologous HSCT applied in the base case (based on AR-DRG R06; \$21,087).  | High, favours BSC<br>Application of a weighted cost for allogeneic HSCT of \$123,956 decreased the ICER to \$ <sup>2</sup> /QALY gained.  |
| Time horizon              | 20-year time horizon in the base case  | Moderate-high, favours oral azacitidine<br>15-year time horizon increased the ICER to \$ <sup>1</sup> /QALY gained,<br>10-year time horizon increased the ICER to \$ <sup>1</sup> /QALY gained. |
| OS point of extrapolation | The submission used extrapolated OS curve data from cycle 69 (63 months or 5.3 years) onwards until the end of time horizon in the base-case analysis. | Moderate, favours oral azacitidine<br>Extrapolation from median follow-up time (51.7 months or 4.3 years) increased the ICER to \$ <sup>1</sup> /QALY gained.                                   |

Source: Calculated during evaluation. The ICER presented in the submission was amended using amended costs discussed in Section 3.6 of the Commentary

Abbreviations: BSC = best supportive care; HSCT = haematopoietic stem cell transplant; ICER = incremental cost-effectiveness ratio; KM = Kaplan–Meier; OS = overall survival; ToT = time on treatment; QALY = quality adjusted life years; SA = sensitivity analysis.

*The redacted values correspond to the following ranges:*

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

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

6.40 The results of the stepped economic evaluation are presented in Table 13. The submission included two steps based on the time horizon. Step 1 applied a time horizon of 4 years, intended to approximate the within trial period given follow-up of 51.7 months as at the September 2020 data cut-off, with Step 2 applying a time horizon of 20 years.

6.41 These results were based on the proposed effective price of oral azacitidine. The model included the cost of concomitant therapies, supportive care costs, cost of subsequent therapies, cost of adverse events, cost of HSCT and a cost for end-of-life treatment.

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**Table 13: Results of the stepped economic evaluation (effective price)**

|  | Oral azacitidine | BSC  | Increment         | Incremental cost-effectiveness ratio |
|--|------------------|------|-------------------|--------------------------------------|
| <b>Step 1: Time horizon: 4 years (approximated from trial follow-up 51.7 months)</b> |                  |      |                   |                                      |
| Cost (\$)  |                  |      |                   | -                                    |
| RFS  | 1.39             | 0.98 | 0.42              | \$ <sup>1</sup> per RFS-year gained  |
| Life-years   | 2.16             | 1.74 | 0.42              | \$ <sup>1</sup> per life-year gained |
| QALYs  | 1.55             | 1.20 | 0.35              | \$ <sup>2</sup> per QALY gained      |
| <b>Step 2: Time horizon (20 years)<sup>2</sup></b>                                   |                  |      |                   |                                      |
| Cost (\$)  |                  |      |                   | -                                    |
| RFS  | 2.01             | 1.37 | 0.64 <sup>a</sup> | \$ <sup>3</sup> per RFS-year gained  |
| Life-years   | 3.17             | 2.51 | 0.66              | \$ <sup>4</sup> per life-year gained |
| QALYs  | 2.27             | 1.72 | 0.54              | \$ <sup>4</sup> per QALY gained      |

Source: Table 80, p130 of the submission.

Abbreviations: BSC = best supportive care; ICER = incremental cost-effectiveness ratio; OS = overall survival; QALY = quality-adjusted life year; RFS= relapse-free survival.

Note: The ICERs were adjusted during evaluation based on the costs that were incorrectly applied in the model: treatment administration cost (corrected from \$█ to \$█), adverse events costs (corrected from \$█ to \$█ for the oral azacitidine arm and from \$█ to \$█ for the BSC arm), and subsequent therapies costs (corrected from \$█ to \$█ in the oral azacitidine arm and from \$█ to \$█ in the BSC arm) as per the descriptions in Section 3.6 of the Commentary. The submission's (uncorrected) base case ICER was \$75,000 to < \$95,000/QALY gained.

a Incorrectly reported as 1.45 in the submission.

The redacted values correspond to the following ranges:

<sup>1</sup>\$95,000 to < \$115,000

<sup>2</sup>\$115,000 to < \$135,000

<sup>3</sup>\$55,000 to < \$75,000

<sup>4</sup>\$75,000 to < \$95,000

6.42 The average number of events per patient in QUAZAR compared to the economic model are presented in Table 14.

**Table 14: Mean estimates in the trial versus the economic model**

|                    | QUAZAR<br>(median follow-up 51.7 months) |      |           | Economic model<br>(4 years) |      |           | Economic model<br>(20 years) |      |           |
|--------------------|--|------|-----------|-----------------------------|------|-----------|------------------------------|------|-----------|
|                    | Oral AZA                                 | BSC  | Increment | Oral AZA                    | BSC  | Increment | Oral AZA                     | BSC  | Increment |
| RFS (undiscounted) | 0.85                                     | 0.40 | 0.45      | 1.45                        | 1.02 | 0.42      | 2.38                         | 1.61 | 0.77      |
| LYs (undiscounted) | 2.06                                     | 1.23 | 0.83      | 2.27                        | 1.82 | 0.45      | 3.74                         | 2.95 | 0.79      |

Source: Figure 1, p14, Figure 20, p28 of 'QUAZAR September 2020 Data cut Survival Analysis Technical Appendix' of the submission; workbook "Onureg CUA", worksheet 'Deterministic results', 'Onureg calculations', 'No therapy calculations'.

Abbreviations: AZA = azacitidine; BSC = best supportive care; LYs = life years; RFS = relapse-free survival

6.43 The submission's model estimated that treatment with oral azacitidine would extend RFS by 9.2 months (0.77×12) and add 9.5 months (0.79×12) to a patients' lifetime. The model estimated that the average drug cost for oral azacitidine would be \$█ (undiscounted).

6.44 The results of key univariate / multivariate sensitivity analyses are summarised in Table 15.

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Table 15: Key sensitivity analyses

|   | Incremental cost (\$) | Incremental QALY | ICER/QALY (\$) | % change |
|---|-----------------------|------------------|----------------|----------|
| <b>Base case</b>  |                       | 0.54             | █ <sup>1</sup> | -        |
| Discount rate (base case 5% costs and outcomes)   |                       |                  |                |          |
| 0% costs and outcomes   |                       | 0.66             | █ <sup>2</sup> | -17.1%   |
| 3.5% costs and outcomes   |                       | 0.47             | █ <sup>1</sup> | -4.9%    |
| Time horizon (base case 20 years)   |                       |                  |                |          |
| 15 years  |                       | 0.53             | █ <sup>1</sup> | +3.0%    |
| Time on treatment (base case censored mean; 18.1 months (20 cycles))  |                       |                  |                |          |
| Time-on-treatment KM curve only   |                       | 0.54             | █ <sup>1</sup> | +18.9%   |
| Time on treatment based on median RFS (10.2 months or 11.09 cycles; median duration of RFS in the azacitidine arm of QUAZAR)  |                       | 0.54             | █ <sup>3</sup> | -39.7%   |
| Utility (base case relapse-free: 0.833 (QUAZAR), relapse: 0.51 (Joshi et al. 2019))   |                       |                  |                |          |
| Relapse free: 0.849 (QUAZAR mean relapse free utility)  |                       | 0.58             | █ <sup>2</sup> | -6.3%    |
| Relapse: 0.62 (Stein et al. 2019)   |                       | 0.55             | █ <sup>1</sup> | -0.4%    |
| Extrapolation (base case RFS: log-logistic; OS: log-normal extrapolation)   |                       |                  |                |          |
| RFS: log-normal (next best fit AIC and BIC)   |                       | 0.57             | █ <sup>1</sup> | -4.5%    |
| OS: log-logistic (next best fit AIC and BIC)  |                       | 0.50             | █ <sup>1</sup> | +6.5%    |
| Extrapolation point (base case OS: 69 cycles; RFS: 35 cycles)   |                       |                  |                |          |
| OS and RFS: 1 cycle   |                       | 0.56             | █ <sup>1</sup> | -3.0%    |
| OS: 55 cycles (median OS follow up)   |                       | 0.50             | █ <sup>1</sup> | +8.0%    |
| Cost of HSCT (base case based on autologous HSCT AR-DRG R06 = \$21,087.42)  |                       |                  |                |          |
| Cost of HSCT based on allogenic HSCT, weighted average AR-RDG R05A and R05B = \$123,956   |                       | 0.54             | █ <sup>2</sup> | -17.6%   |
| HSCT rates per arm (base case 6.3% oral azacitidine, 13.7% BSC)   |                       |                  |                |          |
| 13.7% HSCT rate in both arms*   |                       | 0.54             | █ <sup>1</sup> | +3.8%    |
| <b>Multivariate analysis</b>  |                       |                  |                |          |
| Cost of HSCT based on allogenic HSCT (\$123,956); and 13.7% HSCT rate in both arms*   |                       | 0.54             | █ <sup>1</sup> | +3.8%    |
| Oral azacitidine DPMQ (max quantity 14) = \$█; DOT based on ToT KM curve; Extrapolation of OS curve from 55 cycles (median follow-up); and Cost of HSCT based on allogenic HSCT (\$123,956)   |                       | 0.50             | █ <sup>1</sup> | +12%     |
| Oral azacitidine DPMQ (max quantity 14) = \$█; DOT based on ToT KM curve; Extrapolation of OS curve from 55 cycles (median follow-up); Cost of HSCT based on allogenic HSCT (\$123,956); and 13.7% HSCT rate in both arms   |                       | 0.50             | █ <sup>4</sup> | +35%     |
| <b>ESC suggested base case</b>  |                       |                  |                |          |
| Oral azacitidine DPMQ (max quantity 14) = \$█; Cost of HSCT based on allogenic HSCT (\$123,956); Treatment specific utility values for relapse free survival (azacitidine = 0.846; BSC = 0.853); DOT based on ToT KM curve; and Extrapolation of OS curve from 55 cycles (median follow-up) |                       | 0.50             | █ <sup>1</sup> | +11.1%   |
| <b>Pre-PBAC response base case</b>  |                       |                  |                |          |
| Oral azacitidine DPMQ (max quantity 14) = \$█; Cost of HSCT based on allogenic HSCT (\$123,956); and Treatment specific utility values for relapse free survival (azacitidine = 0.846; BSC = 0.853)   |                       | 0.54             | █ <sup>2</sup> | -16.3%   |

Source: Tables 83, 84, 85 and 86, pp133-137 of the submission.

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Abbreviations: AIC = Akaike's Information Criteria; BIC = Bayesian Information Criteria; BSC = best supportive care; DOT = duration of treatment; DPMQ = dispensed price for maximum quantity; HSCT = haematopoietic stem cell transplantation; ICER = incremental cost effectiveness ratio; KM = Kaplan–Meier; OS = overall survival; RFS = relapse free survival; QALY = quality adjusted life years; ToT = time on treatment.

\* ICERs are the same (\$75,000 to < \$95,000/QALY gained) as the cost of HSCT is modelled as a once off, up-front cost

*The redacted values correspond to the following ranges:*

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

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

<sup>3</sup>\$45,000 to < \$55,000

<sup>4</sup>\$95,000 to < \$115,000

- 6.45 The model was sensitive to specification of time on treatment, and the cost of and proportions of patients receiving a HSCT.
- 6.46 The ESC considered that a revised model should allow the incorporation of treatment specific utility values that are based on the QUAZAR trial data for the relapse free health state. In addition, the ESC considered that a more appropriate base case would:
- apply a maximum quantity of 14 tablets (rather than 21, as per the PSCR);
  - apply Kaplan–Meier time on treatment data from QUAZAR to the oral azacitidine and BSC arms;
  - extrapolate the OS curves from the median follow-up point; and
  - apply the corrected cost of allogenic HSCT.
- 6.47 The pre-PBAC response presented a revised base case which applied a maximum quantity of 14 tablets, applied the corrected cost of allogenic HSCT and incorporated treatment specific utility values based on the QUAZAR trial for the relapse free health state. This resulted in an ICER of \$55,000 to < \$75,000 per QALY. If Kaplan–Meier time on treatment data were also applied and OS curves extrapolated from the median follow-up point as recommended by ESC, the ICER increased to \$75,000 to < \$95,000 per QALY<sup>1</sup>.
- 6.48 The PBAC noted that the costs of post-relapse dose escalation for patients identified with blasts between 5 and 15% did not appear to be included in the economic model.

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<sup>1</sup> The pre-PBAC response stated that the ICER for this scenario would be \$75,000 to < \$95,000 per QALY, but this was using 51.7 months as the extrapolation point, rather than 55 cycles.

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**Drug cost/patient/course**

**Table 16: Drug cost per patient for oral azacitidine**

|                           | <b>Trial dose and duration</b>                          | <b>Model</b>  | <b>Financial estimates</b>               |
|---------------------------|---|---|--|
| Mean dose                 | 285.6 mg <sup>a</sup> per day<br>(14 days/28 day cycle) | 269 mg <sup>b</sup> per day<br>(14 days/28 day cycle)                                       | 300 mg/200 mg                            |
| Mean duration             | 18.1 months<br>19.8 cycles <sup>c</sup>                 | 18.1 months<br>19.68 cycles <sup>d</sup> ,<br>adjustment factor for RFS = 0.81 <sup>e</sup> | 18.1 months<br>17.6 scripts <sup>f</sup> |
| Cost/patient/28-day cycle | \$ <sup>g</sup>   | \$ <sup>g</sup>   | DPMQ:<br>\$ (per script)                 |
| Cost/patient/course       | \$  | \$ <sup>h</sup>   | \$                                       |

Source: Table 37, p59; workbook “Onureg CUA” worksheet “Efficacy” cell D237, worksheet ‘Drug Cost’, cells D8 and J31, of the submission. Compiled during evaluation

Abbreviation: DPMQ = dispensed price per maximum quantity; RFS = relapse free survival.

a: The mean dose as reported in QUAZAR CSR

b: The mean dose used in the economic model is equal to 300 mg \* 89.6% (relative dose intensity as reported in QUAZAR CSR)

c: Mean number of cycles as reported in QUAZAR CSR

d: Mean number of cycles used in the economic model based on mean number of months (18.1), estimated as 19.68 (=18.1\*(365.25/12)/28)

e: The RFS adjustment factor represents the proportion of patients who were relapse free in each cycle up to the censored mean duration of treatment of 18.1 months, as applied in the model

f: The script numbers were estimated based on 18.1 months of treatment and 89.6% compliance rate.

g: DPMQ per 300 mg dose is \$ (DPMQ: \$/21(max quantity units). The cost per cycle was based on assuming 14 days of treatment in each cycle, with the cost per dose multiplied by the number of doses per unit (=mean dose/300 mg)

h: In the economic model an additional RFS adjustment factor of 0.81 is applied given the application in the model of a censored mean treatment duration, resulting in a lower cost per patient.

**Estimated PBS usage & financial implications**

- 6.49 This submission was not considered by DUSC.
- 6.50 The submission presented an epidemiological approach to estimate the utilisation and financial impact of the proposed listing.
- 6.51 There was some uncertainty with the estimation of the proportion of patients that would achieve CR/CRi. The number of patients may be overestimated, details are presented in Table 17.

**Table 17: Key inputs for financial estimates**

| <b>Parameter</b>                               | <b>Value applied and source</b>  | <b>Comment</b> |
|--|--|----------------|
| Incidence population                           | Based on a ratio of projected incident AML patients and Australian population. Estimated incidence was approximately 0.043% based on Australian Cancer Incidence and Mortality Book, specific for AML (AIHW 2021). Linear projection based on data from 1982-2017. | -              |
| Proportion treated with intensive chemotherapy | 61%, published literature for Australian based cohorts. Chua et al. (2020) and Gangatharan et al. (2021).  | -              |

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| Parameter  | Value applied and source  | Comment   |
|--|---|---|
| Proportion achieved CR/CRi                                 | 80%, based on Chua et al. (2020), Australian cohort with FLT3 mutant positive AML, 73% (n=51) achieved CR and 7% (n=5) CRi  | Although the population is based on an Australian cohort, all included patients had an FLT3 mutation. The observed outcomes may not be representative of patients without an FLT3 mutation. Further, the numbers of patients were small (N =70). Chua et al (2020) presented results from the RATIFY placebo arm where 54% (191/357) achieved CR.<br>The submission presented a statement from an AML specialist who stated that approximately 70% of patients achieve remission after intensive chemotherapy. There is significant uncertainty in these estimates. |
| Proportion of FLT3- and FLT3+ not treated with midostaurin | 68.6%, based on 34% FLT3+ (midostaurin PSD, July 2018) plus 7.5% (5 to 10%) of FLT3+ may have side-effects and access oral azacitidine (expert statement: AML specialist).<br>$68.6\% = (100\% - 34\%) + (34\% * 0.075)$  | The submission assumed that patients with FLT3 positive mutation will receive midostaurin in favour of oral azacitidine and that a proportion of these patients will have side effects and may access oral azacitidine.   |
| Patients who are not candidates for HSCT                   | 81.5%, based on a mid-range of (1) 37.5% (30 to 45%, from expert statement) of patients who are fit for intensive chemotherapy (61%) will receive a HSCT (i.e. 77.1%) and (2) Nivison-Smith et al (2019) who found that 79.3% of AML patients do not receive a HSCT. In addition, up to 15% of patients might receive HSCT following oral azacitidine, estimated by clinical expert at maximum of 15%, $(100\% - 78.2\%) * 0.015 = 3.3\%$ | For midostaurin, a SCT rate of 70-80% was accepted (midostaurin PSD, November 2019).  |
| Uptake rate  | █% in Year 1 increasing to █% in Year 6. Based on uptake of midostaurin as proxy, using PBS Authority Required (Written) listings – Tranche 1 report by the Drug Utilisation Sub-Committee (DUSC 2020), which reports the number of patients who initiated midostaurin in the financial years 2018/2019 and 2019/2020 (Table 87).   | -   |
| Dose/duration  | 11.74 scripts estimated based on censored mean duration of 18.1 months and 89.6% compliance rate, based on QUAZAR.  | Applied incorrectly in the submission. PSCR estimates were corrected to include change in maximum quantity (from 21 to 14) and the resultant impact on the number of scripts (from 11.74 to 17.61). The corrections were accepted in the pre-PBAC response.   |

Source: Table 87, p143, Table 88, p144, Tables 89 and 90 p145, Tables 91 and 92, p146 of the submission

Abbreviations: AML = acute myeloid leukemia; CR = complete response; CRi = complete response with incomplete haematologic recovery; FLT3+ = FMS-related tyrosine kinase 3 positive; HSCT = hematopoietic stem cell transplantation; PBS = Pharmaceutical Benefits Scheme.

6.52 A summary of the estimated use and financial implications is presented in Table 18.

6.53 During the evaluation it was noted that the submission applied 11.74 prescriptions (which was the average total number of prescriptions per course of treatment) to the total number of patients (incident + prevalent) in each year, thus overestimating the number of prescriptions from Year 2 onwards. Revised estimates were provided in the

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PSCR. These estimates were further corrected to account for the reduced proposed maximum quantity (14 rather than 21) and the resultant impact on the number of prescriptions (17.61, increased from 11.74) and are also presented in Table 18. The corrections were accepted in the pre-PBAC response.

**Table 18: Estimated use and financial implications (effective price)**

|   | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 | Year 6 |
|---|--------|--------|--------|--------|--------|--------|
| <b>Estimated extent of use as per submission</b>  |        |        |        |        |        |        |
| Number of patients initiating treatment   | 1      | 1      | 1      | 1      | 1      | 1      |
| Total patient years of treatment <sup>a</sup>   | 1      | 1      | 1      | 1      | 1      | 1      |
| Number of prescriptions dispensed <sup>b</sup>  | 2      | 2      | 2      | 3      | 3      | 3      |
| <b>Estimated financial implications of oral azacitidine as per submission</b>   |        |        |        |        |        |        |
| Net cost to PBS/RPBS (less copayments) (\$)   | 4      | 5      | 6      | 6      | 6      | 6      |
| <b>Corrected estimated extent of use (as per PSCR and updated to account for reduced maximum quantity)</b>                              |        |        |        |        |        |        |
| Number of prescriptions dispensed <sup>c</sup>  | 2      | 2      | 2      | 3      | 3      | 3      |
| <b>Corrected estimated financial implications of oral azacitidine (as per PSCR and updated to account for reduced maximum quantity)</b> |        |        |        |        |        |        |
| Net cost to PBS/RPBS (less copayments) (\$)   | 4      | 4      | 5      | 5      | 5      | 5      |

Source: Table 89, p145, Table 90, p 145, Table 91, p146, Table 93, p147 of the submission

Notes:

a: The submission estimated patient years in Years 2 to 6 based on the assumed mean duration of treatment of 18.1 months.

b: Assuming 11.74 prescriptions per treatment duration as estimated by the submission, based on the mean duration of treatment of 18.1 months, assuming 21 packs of oral azacitidine per prescription and a compliance rate of 0.896 (based on relative dose intensity in QUAZAR).

c: Updated from results presented in the PSCR to account for reduced maximum quantity (14, instead of 21) and the associated change in the total number of prescriptions per treatment duration (17.61, instead of 11.74).

The redacted values correspond to the following ranges:

<sup>1</sup>< 500

<sup>2</sup>500 to < 5000

<sup>3</sup>5000 to < 10,000

<sup>4</sup>\$0 to < \$10 million

<sup>5</sup>\$10 million to < \$20 million

<sup>6</sup>\$20 million to < \$30 million

6.54 The corrected PSCR estimates, updated to account for the reduction in the proposed maximum quantity, estimated that the total cost to the PBS/RPBS of listing oral azacitidine was \$10 million to < \$20 million in Year 6, and \$70 million to < \$80 million over the first 6 years of listing.

6.55 The submission assumed that 81.5% of patients would not receive a HSCT, based on:

- Advice from an AML clinician that 30 to 45% (the mid-point of 37.5% was used) of those patients who are fit for intensive chemotherapy (61%) would receive a HSCT (i.e. 77.1% of all AML patients), which aligned with Nivison-Smith et al (2019) who found that 79.3% of AML patients in Australia and New Zealand between 2005 and

2013 did not receive a HSCT. The submission used the mid-point of these two estimates (78.2%). The PBAC noted that Nivison-Smith et al (2019) was based on patients treated between 2005 and 2013 and may not reflect the increasing use of haploidentical transplant;

- In addition, the submission stated that because oral azacitidine provides a longer opportunity to find a suitable donor for HSCT due to the extension in OS and RFS, a further 15% (based on expert opinion) of those patients who did not have a transplant prior to commencing oral azacitidine may become suitably fit with time and be eligible for a transplant following oral azacitidine treatment. The submission estimated that a total of 3.3% of patients become eligible for transplant after receiving oral azacitidine based on:  $(100\% - 78.2\%) \times 15\% = 3.3\%$ . The rationale for adding these patients to the eligible population was unclear.

- 6.56 The submission presented a number of sensitivity analyses by varying the input values  $\pm 10\%$  for the following parameters: proportion of patients treated with intensive chemotherapy, proportion of patients with FLT3- and FLT3+ treated with midostaurin, proportion of patients that achieve CR/CRi, proportion of patients that do not receive HSCT and the assumed uptake rate per year. The sensitivity analyses resulted in changes of between  $\pm 11\%$  to  $\pm 33\%$ . A sensitivity analysis conducted during the evaluation applying a CR/CRi rate of 54% (from Chua et al., 2020) showed that there was a 32% decrease in cost to the PBS/RPBS compared to the base case.
- 6.57 The ESC considered that time on treatment should be consistent between the economic model and financial estimates, i.e. based on Kaplan–Meier data from the QUAZAR trial. The PBAC noted that this inconsistency would be resolved if the treatment duration in the economic model were corrected (refer to paragraph 6.37).

### **Quality Use of Medicines**

- 6.58 The submission stated that there have been no safety concerns identified in clinical studies specific to the oral formulation of azacitidine. In addition, the injectable form of azacitidine has been registered and PBS listed for use in Australia since 2009, with a well-known safety profile. The submission stated that routine pharmacovigilance is considered adequate for oral azacitidine.
- 6.59 The approved Product Information stipulates that oral azacitidine should not be used interchangeably with injectable azacitidine due to differences in the exposure, dose and schedule of treatment. Despite this statement, there is a possibility of use in patients for whom injectable azacitidine is PBS subsidised, including those with del-5q myelodysplastic syndrome where there is no published data on the use of oral azacitidine.

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

- 6.60 The submission stated that the sponsor is willing to enter a risk-sharing arrangement (RSA) related to expenditure in this disease state, including the potential for subsidisation caps.

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

## **7 PBAC Outcome**

- 7.1 The PBAC did not recommend oral azacitidine as maintenance therapy in patients with acute myeloid leukaemia (AML) who achieve complete remission (CR) or complete remission with incomplete blood count recovery (CRi) following induction chemotherapy with or without consolidation treatment, and who are not candidates for, including those who choose not to proceed to, haematopoietic stem cell transplantation (HSCT). Although the PBAC was satisfied that oral azacitidine provides, for some patients, a significant improvement in efficacy including improved overall survival (OS) and relapse free survival (RFS), the PBAC considered that changes to the economic model parameters, including a reduction to the price of oral azacitidine, would be required to achieve acceptable incremental cost-effectiveness. Further, the PBAC considered that the financial implications were overestimated.
- 7.2 The PBAC considered that there was a high unmet need for effective therapies to treat this condition.
- 7.3 The PBAC considered that the proposed place in therapy was reasonable and that the proposed treatment algorithm was largely consistent with current practice in Australia.
- 7.4 The PBAC noted that the proposed restriction did not align with the inclusion criteria of the QUAZAR trial as it did not restrict access to oral azacitidine on the basis of cytogenetic risk. The PBAC considered that the restriction should only allow treatment in patients with intermediate- or poor-risk cytogenetics (i.e. exclude patients with favourable-risk cytogenetics) to align with the enrolment criteria of the QUAZAR trial and with the National Comprehensive Cancer Network guidelines. Further the PBAC considered that, as patients with favourable risk have a high cure rate with intensive chemotherapy without HSCT, the availability of oral azacitidine in this patient group may result in unnecessary treatment and toxicity.
- 7.5 The PBAC noted that the QUAZAR trial allowed dose escalation for patients with disease relapse (i.e. blasts of 5-15% in either the peripheral blood or bone marrow), with the aim of continuing treatment and re-initiating remission. The 'dose escalation' extended the dosage schedule from 14 days to 21 days of repeated 28-day treatment cycles. The PBAC noted that such use is inconsistent with the restrictions for other AML therapies (which have defined progressive disease as > 5% blasts in the marrow) and inconsistent with the clinical positioning of oral azacitidine as maintenance

therapy (a therapy given post CR/CRi). Further, the PBAC considered that it was unclear if the results of the QUAZAR trial could be generalised for the purpose of reinitiating remission. However, the PBAC also noted that 21% of patients in the oral azacitidine arm of the QUAZAR trial received a dose escalation at AML relapse and that the benefits of such use were captured in the efficacy results of the trial and were thus incorporated in the efficacy inputs in the economic model. However, the PBAC noted that the costs of such use did not appear to be incorporated into the base case of the economic model, but also acknowledged that in clinical practice patients are unlikely to have bone marrow biopsies as frequently as in the trial, thus the relative number of patients identified with blasts between 5 and 15% may be lower. The PBAC considered that, if post-relapse dose escalation were to be permitted under the PBS, then the risk of such use not being cost-effective would need to be managed, for example through an RSA. Further, the PBAC considered that a separate restriction would be required for such use to ensure oral azacitidine is used as a continuing therapy (not an initial therapy) in this context.

- 7.6 In terms of the proposed restrictions the PBAC agreed with the advice provided by the ESC in paragraphs 3.9 to 3.11, and also considered that:
- the initial supply restriction should be Authority Required (telephone/online) with continuing supply available as an Authority Required (Streamlined) to align with injectable azacitidine;
  - the restrictions should include a caution stating that oral azacitidine should not be used interchangeably with injectable azacitidine due to differences in the exposure, dose and schedule of treatment; and
  - the restrictions should include an appropriate caution regarding pregnancy given that azacitidine is a Category X drug.
- 7.7 The PBAC considered that the nominated comparator of best supportive care (BSC) was appropriate.
- 7.8 The PBAC considered that the claim that oral azacitidine demonstrated superior efficacy compared to BSC in the key clinical trial, QUAZAR, was reasonable. The PBAC noted that treatment with oral azacitidine was associated with a statistically significant improvement in OS with a median OS in the oral azacitidine arm of 24.7 months compared to 14.8 months in the BSC arm (HR = 0.69; 95% CI: 0.56, 0.86) at a median follow-up of 51.7 months. RFS was also statistically significantly improved in the oral azacitidine arm (10.2 months) compared to the BSC arm (4.8 months; HR = 0.65; 95% CI: 0.52, 0.81).
- 7.9 The PBAC considered that the claim that oral azacitidine was inferior in terms of safety compared to BSC was reasonable, noting that oral azacitidine was associated with higher rates of Grade  $\geq$  3 treatment-emergent adverse events (TEAEs) and TEAEs resulting in treatment discontinuation.

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- 7.10 The PBAC noted that the submission claimed that oral azacitidine was noninferior to BSC in terms of health-related quality of life (HRQoL). The PBAC considered that although there were no statistically significant or clinically meaningful differences between the oral azacitidine and BSC arms in terms of changes from baseline in either the EQ-5D-3L instrument or the FACIT-Fatigue scale at Cycle 34, it was difficult to conclude noninferiority given:
- HRQoL change from baseline appeared to be superior in the BSC arm compared to the oral azacitidine arm at various time points throughout the follow-up period;
  - the number of patients remaining available to make HRQoL assessments over time decreased; and
  - the adverse event profile of oral azacitidine and the claim of inferior safety.
- 7.11 The submission presented a cost-utility analysis comparing oral azacitidine to BSC applying data from the QUAZAR trial with a base case ICER of \$75,000 to < \$95,000 per quality adjusted life year (QALY).
- 7.12 The PBAC noted the following issues with the submission’s economic model:
- The same utility value was applied to both treatment arms in the relapse free health state (paragraph 6.38). The PBAC considered that this was not adequately justified given the adverse event profile of oral azacitidine (paragraph 7.7).
  - The incorrect cost of HSCT was applied as it was based on autologous rather than allogenic transplants (paragraph 6.37). The PBAC noted that the correct cost was \$123,956.
  - The way that the average treatment duration was applied resulted in an average treatment duration of 15 months being estimated, rather than 18.1 months (paragraph 6.35). The PBAC considered that applying the Kaplan–Meier time on treatment data from QUAZAR, which resulted in the patients receiving an average of 18 months treatment, was appropriate.
  - The point of extrapolation of the OS curves (paragraph 6.33). The PBAC noted that the OS curves were extrapolated from 69 cycles at which point 6.7% of patients in the oral azacitidine arm and 5.1% of patients in the BSC arm were at risk. The PBAC noted that the data at this point may have been unreliable due to significant censoring and small numbers of patients remaining event-free. The PBAC considered that it would be more appropriate to extrapolate OS from an earlier time point where the Kaplan–Meier curves are more reliable, and for example noted that at the median follow-up point (55 cycles), 16% of patients in the oral azacitidine arm and 10% of patients in the BSC arm remained at risk, and considered this would be a more appropriate time point from which to extrapolate.
- 7.13 The PBAC noted that the pre-PBAC response provided a revised base case which

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applied the corrected cost of allogenic HSCT and treatment specific utility weights to the relapse free health state and resulted in an ICER of \$55,000 to < \$75,000 per QALY. The PBAC considered that an appropriate base case would also apply the Kaplan–Meier time on treatment data from the QUAZAR trial and extrapolate the OS curves from the median follow-up point. The PBAC noted that, under this scenario, the ICER would increase to \$75,000 to < \$95,000 per QALY. The PBAC considered that an ICER of approximately \$55,000 to < \$75,000 per QALY would be acceptably cost-effective and noted that a price reduction would be required to achieve this ICER.

- 7.14 The PBAC considered that the financial impact of listing oral azacitidine was overestimated, noting that the submission estimated that in Year 6 approximately 25% of all AML patients would be initiating treatment with oral azacitidine. The PBAC considered that the proportion of patients who achieved CR/CRi applied in the submission of 80% was likely overestimated as it was based on a small cohort of younger patients (18 to 64 years) with an FLT3 mutation only. The PBAC considered this cohort of patients was likely to have higher response rates than the requested PBS population. Further, the PBAC noted that other trial results and expert opinion estimated a rate of CR/CRi of 54% to 70% and considered that this would be a more appropriate range for estimating the proportion of patients achieving a CR/CRi, but that this would be further reduced in patients with intermediate- or poor-risk cytogenetics.
- 7.15 The PBAC also considered that the proportion of patients who would not be candidates for, or who would choose not to undergo, HSCT of 81.5% was overestimated. The PBAC noted that a rate of 70% to 80% was accepted for midostaurin in 2017 (paragraph 6.48, midostaurin PSD, November 2017 PBAC Meeting), and further considered that the increasing use of haploidentical transplant would result in a higher proportion of fit patients having donors and thus receiving a HSCT. Overall, the PBAC considered that, based on current practices, the proportion of patients who do not undergo a HSCT is likely to be at the lower end of the range accepted for midostaurin (i.e. close to 70%).
- 7.16 The PBAC considered that the financial estimates would also need to be revised to align with its advice that the listing should restrict use to patients with intermediate- or poor-risk cytogenetics only (i.e. exclude those with favourable-risk cytogenetics). The PBAC considered that the other changes to the restriction were unlikely to materially impact patient numbers.
- 7.17 The PBAC considered that the outstanding issues could be easily resolved in a simple resubmission for oral azacitidine. The PBAC also considered that oral azacitidine addresses a high and urgent unmet clinical need and was expected to provide a substantial and clinically relevant improvement in efficacy over any alternative therapies. Therefore, the PBAC considered an early resolution pathway would be acceptable. If the sponsor accepts this pathway, then the following changes may address these outstanding issues without requiring further re-evaluation:

- a revised restriction that incorporates the changes suggested in paragraphs 7.4 and 7.6;
- address the issues around dose escalation for patients who experience disease relapse while on oral azacitidine, in particular managing the risk of such use not being cost-effective, for example through a RSA (per paragraph 7.5). An alternative way to manage this risk could be through incorporating dose escalation into the base case of the economic model (noting the PBAC’s advice that an ICER of approximately \$55,000 to < \$75,000 per QALY would be acceptably cost-effective);
- a revised economic model that incorporates the changes outlined in paragraph 7.13 and results in an ICER of approximately \$55,000 to < \$75,000 per QALY; and
- revised financial impact estimates which incorporate the changes outlined in paragraphs 7.14, 7.15 and 7.16.

The early resolution resubmission must be lodged by week 7 of the current PBAC cycle or the next cycle. If the issues cannot be addressed by the sponsor in a simple resubmission and the early resolution timing is not acceptable, a standard re-entry pathway is available.

7.18 The PBAC noted that this submission is eligible for an Independent Review.

**Outcome:**

Not recommended

## **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**

The Sponsor welcomes the PBAC’s decision to resubmit via an early resolution pathway and looks forward to continuing to work with the PBAC and the Department of Health to provide access of oral azacitidine (Onureg) to patients.

**Addendum to the July 2022 PBAC PSD:**

**7.01 AZACITIDINE,  
Tablet 200 mg, Tablet 300 mg,  
Onureg<sup>®</sup>,  
Celgene Pty Limited.**

**10 Background**

- 10.1 The resubmission requested a Section 85 (General Schedule) listing for oral azacitidine for maintenance therapy in certain patients with acute myeloid leukaemia (AML) who are not candidates for, including those who choose not to proceed to, haematopoietic stem cell transplantation (HSCT).
- 10.2 The resubmission was made under the early resolution pathway and sought to address the PBAC's concerns from its July 2022 meeting.

**11 Consideration of the evidence**

- 11.1 In July 2022 the PBAC considered the outstanding issues could be resolved in a simple resubmission. The PBAC considered that if the following issues were addressed, then the resubmission would not require further re-evaluation:
- a revised restriction that incorporates the changes suggested in paragraphs 7.4 and 7.6;
  - address the issues around dose escalation for patients who experience disease relapse while on oral azacitidine, in particular managing the risk of such use not being cost-effective, for example through a RSA (per paragraph 7.5). An alternative way to manage this risk could be through incorporating dose escalation into the base case of the economic model (noting the PBAC's advice that an ICER of approximately \$55,000 to < \$75,000 per QALY would be acceptably cost-effective);
  - a revised economic model that incorporates the changes outlined in paragraph 7.13 and results in an ICER of approximately \$55,000 to < \$75,000 per QALY; and
  - revised financial impact estimates which incorporate the changes outlined in paragraphs 7.14, 7.15 and 7.16.
- 11.2 Table 19 summarises how the resubmission addressed each of these issues.

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**Table 19: Summary of changes made in the resubmission**

| <b>Outstanding issues from the July 2022 PBAC PSD</b>  | <b>How the issue was addressed in the early resolution resubmission</b>  |
|--|--|
| A reduction to the price would be required to achieve an acceptable ICER (Para 7.1).   | The resubmission reduced the AEMP of oral azacitidine by 16.6% (effective AEMP was reduced from \$█████ to \$█████). This was further reduced following the identification of an error in the model post PBAC consideration to \$█████ (see paragraph 11.5).   |
| <b>Restriction</b>   |  |
| The initial supply restriction should be Authority Required (telephone/online) with continuing supply available as an Authority Required (Streamlined) (Para 7.6).   | Authority Required (Telephone/online) for Initial Authority Required (Streamlined) for Continuing  |
| A separate restriction would be required for dose escalation in disease relapse to ensure oral azacitidine is used as a continuing therapy (not an initial therapy) in this context (Para 7.5).  | A separate Authority required (Written) restriction was proposed for dose escalation that allowed use in patients with 5% to 15% blasts who had already received oral azacitidine.   |
| The restriction should: <ul style="list-style-type: none"> <li>- only allow treatment in patients with intermediate- or poor-risk cytogenetics (Para 7.4);</li> <li>- include a caution that oral azacitidine should not be used interchangeably with injectable azacitidine (Para 7.6);</li> <li>- include a caution regarding pregnancy (Para 7.6).</li> </ul> | The restriction was revised as requested (see Section 12 – Requested listing)  |
| <b>Economic model</b>  |  |
| The economic model should: <ul style="list-style-type: none"> <li>- apply the Kaplan–Meier time on treatment data from the QUAZAR trial (Para 7.13)</li> <li>- extrapolate the OS curves from the median follow-up (Para 7.13)</li> <li>- result in an ICER of approximately \$█████<sup>1</sup> per QALY<sup>a</sup> (Para 7.13)</li> </ul>                     | Structural changes were made as requested. In addition, the AEMP of oral azacitidine was reduced by 16.6%. The resultant ICER was \$█████ <sup>1</sup> /QALY (resubmission stated that, using the 2021 dispensing fees, the ICER would be exactly \$█████ <sup>1</sup> /QALY). The model was further revised post PBAC consideration following the identification of an error (see paragraph 11.5) |
| Ensure cost-effectiveness of oral azacitidine in dose escalation (Para 7.5).   | The resubmission argued that the economic model already accounted for the costs of dose escalation as it applied the relative dose intensity (89.6%) reported in the QUAZAR trial, which incorporated the 25% of patients who had a dose reduction due to AEs, and the 21.6% who had a dose escalation.  |
| <b>Financial estimates</b>   |  |
| The financial impact was overestimated (Paras 7.14, 7.15 and 7.16).  | The net cost to R/PBS was reduced from \$█████ <sup>2</sup> over 6 years (in the July 2022 pre-PBAC response) to \$█████ <sup>3</sup> over 6 years in resubmission. This was amended to \$█████ <sup>3</sup> over 6 years following correction of the modelling error (see paragraph 11.9 and Table 21).   |
| The submission estimated that in Year 6 approximately 25% of all AML patients would initiate oral azacitidine (Para 7.14).   | The resubmission estimated that in Year 6 approximately 13% of all AML patients would initiate oral azacitidine.   |
| The proportion of patients who achieved CR/CRi should be reduced from 80% to be in the range of 54% to 70%, noting that this proportion would be further reduced in patients with intermediate- or poor-risk cytogenetics (Para 7.14)  | Change made as requested. The proportion of patients who achieved CR/CRi was reduced to 54%.   |
| The proportion of patients who would not be candidates for, or who would choose not to undergo, HSCT should be reduced from 81.5% to close to 70% (Para 7.15).   | Change made as requested. The proportion was reduced to 70%.   |

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| Outstanding issues from the July 2022 PBAC PSD  | How the issue was addressed in the early resolution resubmission  |
|---|---|
| Restrict use to patients with intermediate- or poor-risk cytogenetics only (i.e., exclude those with favourable-risk cytogenetics) (Para 7.16)  | The resubmission assumed 90.9% of patients had intermediate- or poor-risk cytogenetics <ul style="list-style-type: none"> <li>• Source: the Australasian Leukaemia &amp; Lymphoma Group (ALLG) National Blood Cancer Registry (NBCR) 2020 Report for patients aged 50-70 years with de novo AML receiving induction chemotherapy, as reported in the gemtuzumab ozogamicin PSD from the November 2021 PBAC Meeting (PBAC, 2021)</li> </ul>                            |
| <b>RSA</b>  |   |
| The PBAC considered that, if post-relapse dose escalation were to be permitted under the PBS, then the risk of such use not being cost-effective would need to be managed, for example through an RSA (Para 7.5). | An RSA was proposed to manage the risk of dose escalation exceeding that which was seen in the trial (21.40% of patients received a dose escalation). The resubmission stated “for any utilisation in excess of this, the Sponsor is willing to rebate so that the AEMP for 21 tablets would be reduced from \$█ to \$█, which is the cost-effective price for 14 tablets.” This was revised to \$█ following correction of the modelling error (see paragraph 11.5). |

AEMP = approved ex-manufacturer price; CR = complete remission; CRi = complete remission with incomplete blood count recovery; HSCT = haemopoietic stem cell transplant; ICER = incremental cost effectiveness ratio; OS = overall survival; QALY = quality-adjusted life year; RSA = risk sharing arrangement

<sup>a</sup> The pre-PBAC response revised model had already incorporated the following changes: use of treatment specific utilities (i.e. disutility for oral azacitidine); maximum quantity of 14 tables; and correction of the cost of allogenic HSCT.

All paragraph references refer to azacitidine PSD, July 2022 PBAC Meeting.

*The redacted values correspond to the following ranges:*

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

<sup>2</sup>\$70 million to < \$80 million

<sup>3</sup>\$30 million to < \$40 million

## **Economic analysis**

11.3 The resubmission stated that the following inputs were changed in the economic model:

- time on treatment was based on the Kaplan–Meier curves from the QUAZAR trial; and
- the OS curves were extrapolated from the median follow-up.

11.4 The resubmission stated the above changes, in conjunction with the proposed price reduction (an effective AEMP of \$<sup>1</sup> was applied), resulted in an ICER of \$55,000 to < \$75,000 per QALY as shown in Table 20 (if the 2021 PBS fees and mark-ups were applied, the ICER would be exactly \$55,000 to < \$75,000 per QALY). The PBAC noted these changes were consistent with the July 2022 PBAC PSD (paragraph 7.13).

11.5 Following the PBAC meeting, the sponsor advised that there was an error in the time on treatment applied in the model. In the data applied, patients were incorrectly marked as having discontinued treatment instead of being censored. This resulted in a shorter duration of therapy being modelled (restricted mean = 18.1 months) from the trial compared to the extrapolated time on treatment (mean = 26.6 months). As

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using the corrected time on treatment increased the ICER to \$75,000 to < \$95,000 per QALY gained, the sponsor proposed a revised effective AEMP of \$█, which resulted in an ICER of \$55,000 to < \$75,000 per QALY gained.

**Table 20: Results of the economic evaluation**

|            | Oral azacitidine | BSC  | Increment | Incremental cost-effectiveness ratio  |
|------------|------------------|------|-----------|---------------------------------------|
| Cost       | \$█              | \$█  | \$█       | -                                     |
| Life-years | 3.12             | 2.52 | 0.60      | \$█ <sup>1</sup> per life-year gained |
| QALYs      | 2.27             | 1.75 | 0.51      | \$█ <sup>1</sup> per QALY gained      |

Source: 'Section 3 Onureg Workbook Early Resolution Pathway.xlsx' with price and utility inputs updated as outlined in resubmission  
 BSC = best supportive care; ICER = incremental cost-effectiveness ratio; OS = overall survival; QALY = quality-adjusted life year.

The redacted values correspond to the following ranges:  
<sup>1</sup>\$55,000 to < \$75,000

11.6 In July 2022, the PBAC stated that a resubmission should “address the issues around dose escalation for patients who experience disease relapse while on oral azacitidine, in particular managing the risk of such use not being cost-effective, for example through a RSA. An alternative way to manage this risk could be through incorporating dose escalation into the base case of the economic model” (paragraph 7.17, azacitidine PSD, July 2022 PBAC Meeting). The resubmission argued that the economic model already accounted for the costs of dose escalation as it applied the relative dose intensity (89.6%) reported in the QUAZAR trial, which incorporated 25% of patients whose dose was reduced due to adverse events, and 21.6% whose dose was increased, with the majority of dose increases being to treat disease relapse. As such, the resubmission stated that further incorporation of dose escalations in the economic model was not required and would result in the model ‘double counting’ dose escalations.

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

11.7 The resubmission stated that the following parameters were changed in the financial estimates in line with the PBAC’s advice in paragraphs 7.14 to 7.16 of the azacitidine PSD (July 2022 PBAC Meeting):

- the proportion of patients who achieved CR/CRi was reduced from 80% to 54%;
- the proportion of patients who would not be candidates for, or who would choose not to undergo, HSCT was reduced from 81.5% to 70%;
- 90.9% of patients were estimated to have intermediate- or poor-risk cytogenetics. This was based on the Australasian Leukaemia & Lymphoma Group (ALLG) National Blood Cancer Registry (NBCR) 2020 Report for patients aged 50-70 years with de novo AML receiving induction chemotherapy, as reported in the gemtuzumab ozogamicin PSD from the November 2021 PBAC Meeting. This was a new input to align with the PBAC’s suggested changes to the restriction; and
- the lower proposed price was incorporated.

11.8 A summary of the revised estimated use and financial implications is presented in Table 21. As an early resolution resubmission, these changes were not evaluated.

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11.9 The table also includes the revised estimates, which were supplied by the sponsor post PBAC consideration and included the increased time on treatment (mean = 26.6 months) and reduced effective price of oral azacitidine (DPMQ = \$<sup>1</sup>) as compared to \$<sup>3</sup> in the resubmission).

Table 21: Estimated use and financial implications in early resolution resubmission

|  | Year 1           | Year 2           | Year 3           | Year 4           | Year 5           | Year 6           |
|--|------------------|------------------|------------------|------------------|------------------|------------------|
| Number of patients initiating treatment                      | █ <sup>1</sup>   | █ <sup>1</sup>   | █ <sup>1</sup>   | █ <sup>1</sup>   | █ <sup>1</sup>   | █ <sup>1</sup>   |
| <b>Number of prescriptions dispensed</b>                     |                  |                  |                  |                  |                  |                  |
| For initial and continuing (i.e. 300 mg and 200 mg x 14)     | █ <sup>1</sup>   | █ <sup>2</sup>   | █ <sup>2</sup>   | █ <sup>2</sup>   | █ <sup>2</sup>   | █ <sup>2</sup>   |
| For dose escalation (i.e. 300 mg x 21)                       | █ <sup>1</sup>   | █ <sup>1</sup>   | █ <sup>1</sup>   | █ <sup>1</sup>   | █ <sup>2</sup>   | █ <sup>2</sup>   |
| <b>Cost to R/PBS</b>   |                  |                  |                  |                  |                  |                  |
| For initial and continuing                                   | \$█ <sup>3</sup> | \$█ <sup>3</sup> | \$█ <sup>3</sup> | \$█ <sup>3</sup> | \$█ <sup>3</sup> | \$█ <sup>3</sup> |
| For dose escalation  | \$█ <sup>3</sup> | \$█ <sup>3</sup> | \$█ <sup>3</sup> | \$█ <sup>3</sup> | \$█ <sup>3</sup> | \$█ <sup>3</sup> |
| <b>Net cost to PBS/RPBS</b>                                  | \$█ <sup>3</sup> | \$█ <sup>3</sup> | \$█ <sup>3</sup> | \$█ <sup>3</sup> | \$█ <sup>3</sup> | \$█ <sup>3</sup> |
| <b>Post PBAC revised estimates</b>                           |                  |                  |                  |                  |                  |                  |
| Number of patients initiating treatment                      | <sup>1</sup>     | <sup>1</sup>     | <sup>1</sup>     | <sup>1</sup>     | <sup>1</sup>     | <sup>1</sup>     |
| <b>Number of prescriptions dispensed</b>                     |                  |                  |                  |                  |                  |                  |
| For initial and continuing (i.e. 300 mg and 200 mg x 14)     | <sup>1</sup>     | <sup>2</sup>     | <sup>2</sup>     | <sup>2</sup>     | <sup>2</sup>     | <sup>2</sup>     |
| For dose escalation (i.e. 300 mg x 21)                       | <sup>1</sup>     | <sup>1</sup>     | <sup>2</sup>     | <sup>2</sup>     | <sup>2</sup>     | <sup>2</sup>     |
| <b>Cost to R/PBS</b>   |                  |                  |                  |                  |                  |                  |
| For initial and continuing                                   | \$█ <sup>3</sup> | \$█ <sup>3</sup> | \$█ <sup>3</sup> | \$█ <sup>3</sup> | \$█ <sup>3</sup> | \$█ <sup>3</sup> |
| For dose escalation  | \$█ <sup>3</sup> | \$█ <sup>3</sup> | \$█ <sup>3</sup> | \$█ <sup>3</sup> | \$█ <sup>3</sup> | \$█ <sup>3</sup> |
| <b>Net cost to PBS/RPBS</b>                                  | \$█ <sup>3</sup> | \$█ <sup>3</sup> | \$█ <sup>3</sup> | \$█ <sup>3</sup> | \$█ <sup>3</sup> | \$█ <sup>3</sup> |
| <b>Estimated extent of use - July 2022 pre-PBAC response</b> |                  |                  |                  |                  |                  |                  |
| Number of patients initiating treatment                      | █ <sup>1</sup>   | █ <sup>1</sup>   | █ <sup>1</sup>   | █ <sup>1</sup>   | █ <sup>1</sup>   | █ <sup>1</sup>   |
| Number of prescriptions dispensed                            | █ <sup>2</sup>   | █ <sup>2</sup>   | █ <sup>2</sup>   | █ <sup>4</sup>   | █ <sup>4</sup>   | █ <sup>4</sup>   |
| <b>Net cost to PBS/RPBS</b>                                  | \$█ <sup>3</sup> | \$█ <sup>3</sup> | \$█ <sup>5</sup> | \$█ <sup>5</sup> | \$█ <sup>5</sup> | \$█ <sup>5</sup> |

Source: Table 18 of July 2022 PBAC PSD; Tables 9 and 11 of resubmission  
Blue shading represents estimates from the previous pre-PBAC response

The redacted values correspond to the following ranges:

<sup>1</sup>< 500

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

<sup>3</sup>\$0 to < \$10 million

<sup>4</sup>5,000 to < 10,000

<sup>5</sup>\$10 million to < \$20 million

11.10 The resubmission estimated that the total cost to the PBS/RPBS of listing oral azacitidine would be \$0 to < \$10 million in Year 6, and \$30 million to < \$40 million over the first 6 years of listing. The revised estimates provided post PBAC resulted in a cost of \$0 to < \$10 million in Year 6 and a cost of \$30 million to < \$40 million over the first 6 years of listing. This was compared with an estimated cost of \$70 million to < \$80 million over 6 years estimated in the previous

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PSCR/pre-PBAC response.

## Financial Management – Risk Sharing Arrangements

11.11 The resubmission proposed an RSA to manage the risk of dose escalation exceeding that which was seen in the trial (21.40% of patients received a dose escalation). The resubmission stated “for any utilisation in excess of this, the Sponsor is willing to rebate so that the effective ex-manufacturer price for 21 tablets would be reduced from \$1 to \$1, which is the cost-effective price for 14 tablets.” Following correction of the error, this would be reduced to \$1.

## 12 Requested listing

12.1 The resubmission proposed the following restrictions.

| MEDICINAL PRODUCT<br>medicinal product pack   | PBS item<br>code | Max. qty<br>packs | Max. qty<br>units | No. of<br>Rpts | Available brands |
|---|------------------|-------------------|-------------------|----------------|------------------|
| AZACITIDINE   |                  |                   |                   |                |                  |
| azacitidine 300 mg tablet, 7  | NEW              | 2                 | 14                | 2              | Onureg           |
| <b>Category / Program:</b> GENERAL – General Schedule (Code GE)   |                  |                   |                   |                |                  |
| <b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners   |                  |                   |                   |                |                  |
| <b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required (Telephone/online) [new/existing code]  |                  |                   |                   |                |                  |
| <b>Condition:</b> Acute Myeloid Leukaemia   |                  |                   |                   |                |                  |
| <b>Indication:</b> Acute Myeloid Leukaemia  |                  |                   |                   |                |                  |
| <b>Treatment Phase:</b> Maintenance therapy – Initial treatment   |                  |                   |                   |                |                  |
| <b>Clinical criteria:</b>   |                  |                   |                   |                |                  |
| Patient must have demonstrated first complete remission or complete remission with incomplete blood count recovery following intensive induction chemotherapy,                          |                  |                   |                   |                |                  |
| <b>AND</b>  |                  |                   |                   |                |                  |
| <b>Clinical criteria:</b>   |                  |                   |                   |                |                  |
| Patient must not be able to complete intensive curative therapy,  |                  |                   |                   |                |                  |
| <b>AND</b>  |                  |                   |                   |                |                  |
| <b>Clinical criteria:</b>   |                  |                   |                   |                |                  |
| Patient must have intermediate- or poor-risk cytogenetics at the time of induction therapy,   |                  |                   |                   |                |                  |
| <b>AND</b>  |                  |                   |                   |                |                  |
| <b>Clinical criteria:</b>   |                  |                   |                   |                |                  |
| Patient must not have undergone a stem cell transplant,   |                  |                   |                   |                |                  |
| <b>AND</b>  |                  |                   |                   |                |                  |
| <b>Clinical criteria:</b>   |                  |                   |                   |                |                  |
| Patient must not be receiving concomitant PBS-subsidised midostaurin.   |                  |                   |                   |                |                  |
| <b>Administrative Advice:</b> No increase in the maximum quantity or number of units may be authorised.   |                  |                   |                   |                |                  |
| <b>Administrative Advice:</b> No increase in the maximum number of repeats may be authorised.   |                  |                   |                   |                |                  |
| <b>Administrative Advice:</b> Special Pricing Arrangements apply.   |                  |                   |                   |                |                  |
| <b>Caution:</b> Oral azacitidine should not be used interchangeably with injectable azacitidine due to differences in the exposure, dose and schedule of treatment.                     |                  |                   |                   |                |                  |
| <b>Caution:</b> This is a category X drug and must not be given to pregnant women. Pregnancy must be avoided during treatment and for at least 6 months following cessation of therapy. |                  |                   |                   |                |                  |

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| MEDICINAL PRODUCT<br>medicinal product pack   | PBS item<br>code | Max. qty<br>packs | Max. qty<br>units | No. of<br>Rpts | Available brands |
|---|------------------|-------------------|-------------------|----------------|------------------|
| AZACITIDINE   |                  |                   |                   |                |                  |
| azacitidine 300 mg tablet, 7  | NEW              | 2                 | 14                | 2              | Onureg           |
| Azacitidine 200 mg tablet, 7  | NEW              | 2                 | 14                | 2              | Onureg           |
| <b>Category / Program:</b> GENERAL – General Schedule (Code GE)   |                  |                   |                   |                |                  |
| <b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners   |                  |                   |                   |                |                  |
| <b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required – Streamlined [new/existing code]   |                  |                   |                   |                |                  |
| <b>Condition:</b> Acute Myeloid Leukaemia   |                  |                   |                   |                |                  |
| <b>Indication:</b> Acute Myeloid Leukaemia  |                  |                   |                   |                |                  |
| <b>Treatment Phase:</b> Maintenance therapy – Continuing treatment  |                  |                   |                   |                |                  |
| <b>Clinical criteria:</b>   |                  |                   |                   |                |                  |
| Patient must have previously received PBS-subsidised treatment with this drug for this condition,   |                  |                   |                   |                |                  |
| <b>AND</b>  |                  |                   |                   |                |                  |
| <b>Clinical criteria:</b>   |                  |                   |                   |                |                  |
| Patient must not have > 15% blasts in the bone marrow or peripheral blood not attributable to any other cause than AML.   |                  |                   |                   |                |                  |
| <b>AND</b>  |                  |                   |                   |                |                  |
| <b>Clinical criteria:</b>   |                  |                   |                   |                |                  |
| Patient must not be receiving concomitant PBS-subsidised midostaurin.   |                  |                   |                   |                |                  |
| <b>Administrative Advice:</b> No increase in the maximum quantity or number of units may be authorised.   |                  |                   |                   |                |                  |
| <b>Administrative Advice:</b> No increase in the maximum number of repeats may be authorised.   |                  |                   |                   |                |                  |
| <b>Administrative Advice:</b> Special Pricing Arrangements apply.   |                  |                   |                   |                |                  |
| <b>Caution:</b> Oral azacitidine should not be used interchangeably with injectable azacitidine due to differences in the exposure, dose and schedule of treatment.                     |                  |                   |                   |                |                  |
| <b>Caution:</b> This is a category X drug and must not be given to pregnant women. Pregnancy must be avoided during treatment and for at least 6 months following cessation of therapy. |                  |                   |                   |                |                  |

| MEDICINAL PRODUCT<br>medicinal product pack  | PBS item<br>code | Max. qty<br>packs | Max. qty<br>units | No. of<br>Rpts | Available brands |
|--|------------------|-------------------|-------------------|----------------|------------------|
| AZACITIDINE  |                  |                   |                   |                |                  |
| azacitidine 300 mg tablet, 7   | NEW              | 3                 | 21                | 1              | Onureg           |
| <b>Category / Program:</b> GENERAL – General Schedule (Code GE)  |                  |                   |                   |                |                  |
| <b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners  |                  |                   |                   |                |                  |
| <b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required – (Written) [new/existing code]                                    |                  |                   |                   |                |                  |
| <b>Condition:</b> Acute Myeloid Leukaemia  |                  |                   |                   |                |                  |
| <b>Indication:</b> Acute Myeloid Leukaemia   |                  |                   |                   |                |                  |
| <b>Treatment Phase:</b> Dose escalation therapy – Continuing treatment   |                  |                   |                   |                |                  |
| <b>Clinical criteria:</b>  |                  |                   |                   |                |                  |
| Patient must have previously received PBS-subsidised treatment with this drug for this condition,  |                  |                   |                   |                |                  |
| <b>AND</b>   |                  |                   |                   |                |                  |
| <b>Clinical criteria:</b>  |                  |                   |                   |                |                  |
| Patient must have 5% to 15% blasts in the peripheral blood or bone marrow in order to extend the dose schedule as per the TGA Product Information. |                  |                   |                   |                |                  |
| <b>AND</b>   |                  |                   |                   |                |                  |

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|   |
|---|
| <b>Clinical criteria:</b>   |
| Patient must not be receiving concomitant PBS-subsidised midostaurin.   |
| <b>Administrative Advice:</b> No increase in the maximum number of repeats may be authorised.   |
| <b>Administrative Advice:</b> No increase in the maximum quantity or number of units may be authorised.   |
| <b>Administrative Advice:</b> Special Pricing Arrangements apply.   |
| <b>Caution:</b> Oral azacitidine should not be used interchangeably with injectable azacitidine due to differences in the exposure, dose and schedule of treatment.                     |
| <b>Caution:</b> This is a category X drug and must not be given to pregnant women. Pregnancy must be avoided during treatment and for at least 6 months following cessation of therapy. |

- 12.2 As advised by the PBAC in July 2022, the resubmission proposed a separate restriction for dose escalation to ensure oral azacitidine is used as a continuing therapy (not an initial therapy) in this context (paragraph 7.5, azacitidine PSD, July 2022 PBAC Meeting). The resubmission proposed an Authority Required (Written) restriction for dose escalation to: reduce the risk of use outside the intended population (e.g. blast count above 15%); allow prescribers to provide evidence of 5% to 15% blasts in the peripheral blood or bone marrow in line with the QUAZAR trial; and align with the midostaurin PBS item code for initiating maintenance, which is also written authority.
- 12.3 The resubmission proposed that this dose escalation restriction should have one repeat, allowing for two months of treatment at a time. This aligned with the median number of dose escalated cycles (2.0) in the QUAZAR trial.
- 12.4 The resubmission made the following changes to the restriction which aligned with the those suggested in the July 2022 PBAC PSD:
- restricted use to patients with intermediate- or poor-risk cytogenetics (paragraph 7.4, azacitidine PSD, July 2022 PBAC Meeting);
  - the initial supply restriction was changed to Authority Required (telephone/online). The continuing supply restriction remained Authority Required (Streamlined) (paragraph 7.6, azacitidine PSD, July 2022 PBAC Meeting);
  - included a caution stating that oral azacitidine should not be used interchangeably with injectable azacitidine due to differences in the exposure, dose and schedule of treatment (paragraph 7.6, azacitidine PSD, July 2022 PBAC Meeting);
  - included a caution regarding pregnancy given that azacitidine is a Category X drug. (paragraph 7.6, azacitidine PSD, July 2022 PBAC Meeting);
  - prevented use in patients post HSCT (paragraph 3.9, azacitidine PSD, July 2022 PBAC Meeting);
  - the population criteria specifying use in adult patients only was removed (paragraph 3.10, azacitidine PSD, July 2022 PBAC Meeting); and
  - prevented concomitant use of oral azacitidine and PBS-subsidised midostaurin (paragraph 3.11, azacitidine PSD, July 2022 PBAC Meeting).

- 12.5 The PBAC noted that the resubmission had changed the following criteria:  
“Patient must not be a candidate for, including those who choose not to proceed to, haematopoietic stem cell transplantation”  
to  
“Patient must not be able to complete intensive curative therapy”.
- The PBAC noted that while this change was in line with the TGA indication, it was potentially broader and more open to interpretation than the wording proposed in the previous submission. As such, the PBAC considered this change was not appropriate.
- 12.6 The resubmission proposed listing of the 200 mg strength for continuing use only. This appeared to align with the Product Information which outlines a recommended dose of 300 mg, with dose adjustment for adverse reactions or AML disease relapse.
- 12.7 As per the previous submission, the resubmission sought a SPA for oral azacitidine. The PBAC noted that SPAs are generally not entered for medicines in the F2 formulary such as azacitidine.

### **13 PBAC Outcome**

- 13.1 The PBAC recommended oral azacitidine as maintenance therapy in patients with acute myeloid leukaemia (AML) who achieve complete remission (CR) or complete remission with incomplete blood count recovery (CRi) following induction chemotherapy with or without consolidation treatment, and who are not candidates for, including those who choose not to proceed to, haematopoietic stem cell transplantation (HSCT). The PBAC was satisfied that oral azacitidine provides, for some patients, a significant improvement in efficacy including improved overall survival (OS) and relapse free survival (RFS). The PBAC considered that the resubmission’s changes to the economic model parameters adequately addressed its previous concerns and that oral azacitidine would be acceptably cost-effective at the price proposed in the resubmission. Further, the PBAC considered that the resubmission’s changes to the financial estimates were reasonable.
- 13.2 The PBAC reiterated its previous advice that there is a high unmet need for effective therapies to treat this condition.
- 13.3 The PBAC reiterated its previous advice that the claims of superior efficacy and inferior safety compared to BSC were reasonable. The PBAC recalled that treatment with oral azacitidine was associated with a statistically significant improvement in OS with a median OS in the oral azacitidine arm of 24.7 months compared to 14.8 months in the BSC arm (HR = 0.69; 95% CI: 0.56, 0.86) at a median follow-up of 51.7 months in the QUAZAR trial.

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- 13.4 The PBAC considered that the resubmission had adequately addressed its previous concerns around dose escalation for patients with 5% to 15% blasts through the use of a separate Authority Required (Written) restriction and the proposed RSA. In addition, the PBAC noted that the resubmission had provided further information about how the costs of dose escalation were included in the economic model by applying the relative dose intensity (89.6%) reported in the QUAZAR trial, which incorporated 21.6% of patients whose dose was escalated, the majority of which was due to disease relapse. The PBAC considered this was reasonable.
- 13.5 The PBAC noted that the resubmission's changes to the economic model parameters (see paragraph 11.7) were consistent with the advice from July 2022 PBAC PSD. The PBAC considered that its previous concerns were adequately addressed and that oral azacitidine would be acceptably cost-effective at the price proposed in the resubmission.
- 13.6 The PBAC considered that the resubmission's changes to the financial estimates (see paragraph 11.6) were consistent with its suggestions in the July 2022 PBAC PSD. The PBAC considered that the revised estimated financial impact of listing oral azacitidine was reasonable.
- 13.7 The PBAC noted the proposed risk sharing arrangement (RSA) to manage the risk of oral azacitidine being used for dose escalation in a broader range of patients and circumstances than observed in the trial, and the risk of such use (in the dose escalation setting) not being cost-effective. The PBAC noted that the expenditure caps for use of oral azacitidine in the dose escalation setting, which were based on the 'Cost to R/PBS for dose escalation' in Table 21, were low. The PBAC requested that the DUSC consider a review of the use of oral azacitidine in the dose escalation setting when at least 24 months of prescription data are available and if use was higher than estimated, the implementation of the proposed RSA would be considered. The PBAC advised, that if implemented, rebates for use above the cap should be based on the price for 21 tablets being reduced to the price for 14 tablets (which equates to a rebate of around 1%).
- 13.8 The PBAC considered that most of the changes to the proposed restrictions as outlined in paragraph 10.4 were appropriate with the exception of the continuing supply restriction remaining Authority Required (Streamlined). The PBAC considered that continuing supply should, like initial supply, be an Authority Required (telephone/online) to prevent the risk of usage in the dose escalation setting. The PBAC considered that the inclusion of a separate Authority Required (written/online immediate assessment) restriction for dose escalation would be appropriate.
- 13.9 The PBAC advised that the clinical criteria in the initial supply restriction of 'Patient must not be able to complete intensive curative therapy' should be changed to the more specific wording of 'Patient must not be a candidate for, including those who choose not to proceed to, haematopoietic stem cell transplantation'.

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- 13.10 The PBAC recommended that the Early Supply Rule should apply.
- 13.11 The PBAC advised that oral azacitidine is not suitable for prescribing by nurse practitioners.
- 13.12 The PBAC found that the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were met. Specifically, the PBAC found that in the circumstances of its recommendation for oral azacitidine as maintenance therapy in patients with AML:
- a) The treatment is expected to provide a substantial and clinically relevant improvement in efficacy over BSC on the basis of the OS gain observed in the QUAZAR trial;
  - b) The treatment is expected to address a high and urgent unmet clinical need in the proposed population;
  - c) It would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A on the basis of the preceding findings.
- 13.13 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

**Outcome:**

Recommended

## 14 Recommended listing

14.1 Add new item:

| MEDICINAL PRODUCT<br>medicinal product pack  | PBS item<br>code | Max. qty<br>packs | Max. qty<br>units | No. of<br>Rpts | Available brands |
|--|------------------|-------------------|-------------------|----------------|------------------|
| AZACITIDINE  |                  |                   |                   |                |                  |
| azacitidine 300 mg tablet, 7   | NEW              | 2                 | 14                | 2              | Onureg           |
|  |                  |                   |                   |                |                  |
| <b>Category / Program:</b> GENERAL – General Schedule (Code GE)  |                  |                   |                   |                |                  |
| <b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners  |                  |                   |                   |                |                  |
| <b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required (Telephone/online)   |                  |                   |                   |                |                  |
| <b>Condition:</b> Acute Myeloid Leukaemia  |                  |                   |                   |                |                  |
| <b>Indication:</b> Acute Myeloid Leukaemia   |                  |                   |                   |                |                  |
| <b>Treatment Phase:</b> <del>Maintenance therapy</del> Treatment following intensive induction chemotherapy - Initial treatment                                |                  |                   |                   |                |                  |
| <b>Clinical criteria:</b>  |                  |                   |                   |                |                  |
| Patient must have demonstrated first complete remission or complete remission with incomplete blood count recovery following intensive induction chemotherapy, |                  |                   |                   |                |                  |
| <b>AND</b>   |                  |                   |                   |                |                  |
| <b>Clinical criteria:</b>  |                  |                   |                   |                |                  |
| Patient must not be a candidate for, including those who choose not to proceed to, haematopoietic stem cell transplantation,                                   |                  |                   |                   |                |                  |

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|--|
| <b>AND</b>   |
| <b>Clinical criteria:</b>  |
| Patient must have intermediate- or poor-risk cytogenetics at the time of induction therapy,  |
| <b>AND</b>   |
| <b>Clinical criteria:</b>  |
| Patient must not have undergone a stem cell transplant,  |
| <b>AND</b>   |
| <b>Clinical criteria:</b>  |
| Patient must not be receiving concomitant PBS-subsidised midostaurin.  |
| <b>Administrative Advice:</b> No increase in the maximum quantity or number of units may be authorised.  |
| <b>Administrative Advice:</b> No increase in the maximum number of repeats may be authorised.  |
| <b>Administrative Advice:</b> Special Pricing Arrangements apply.  |
| <b>Caution:</b> Oral azacitidine should not be used interchangeably with injectable azacitidine due to differences in the exposure, dose and schedule of treatment.  |
| <b>Caution:</b> This is a category X drug and must not be given to pregnant women. Pregnancy must be avoided during treatment and for at least 6 months following cessation of therapy.  |
| <b>Prescribing Instruction</b>   |
| <i>A complete remission is defined as bone marrow blasts of less than 5%, absence of blasts with Auer rods, absence of extramedullary disease, independent of blood transfusions and a recovery of peripheral blood counts with peripheral neutrophil count &gt; 1.0 x 10<sup>9</sup>/L and platelet count ≥ 100 x 10<sup>9</sup>/L</i>  |
| <b>Prescribing Instruction</b>   |
| <i>A complete remission with incomplete blood count recovery is defined as bone marrow blasts of less than 5%, absence of blasts with Auer rods, absence of extramedullary disease, independent of blood transfusions and a recovery of peripheral blood counts with peripheral neutrophil count &lt; 1.0 x 10<sup>9</sup>/L or platelet count &lt; 100 x 10<sup>9</sup>/L</i> |
| <b>Administrative Advice:</b>  |
| <i>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 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).</i>                          |

| MEDICINAL PRODUCT<br>medicinal product pack   | PBS item<br>code | Max. qty<br>packs | Max. qty<br>units | No. of<br>Rpts | Available brands |
|---|------------------|-------------------|-------------------|----------------|------------------|
| AZACITIDINE   |                  |                   |                   |                |                  |
| azacitidine 300 mg tablet, 7  | NEW              | 2                 | 14                | 2              | Onureg           |
| Azacitidine 200 mg tablet, 7  | NEW              | 2                 | 14                | 2              | Onureg           |
| <b>Category / Program:</b> GENERAL – General Schedule (Code GE)   |                  |                   |                   |                |                  |
| <b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners   |                  |                   |                   |                |                  |
| <b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required – Streamlined [ <del>new/existing code</del> ] (Telephone/online) |                  |                   |                   |                |                  |
| <b>Condition:</b> Acute Myeloid Leukaemia   |                  |                   |                   |                |                  |
| <b>Indication:</b> Acute Myeloid Leukaemia  |                  |                   |                   |                |                  |
| <b>Treatment Phase:</b> <del>Maintenance therapy</del> Treatment following intensive induction chemotherapy – Continuing treatment                |                  |                   |                   |                |                  |
| <b>Clinical criteria:</b>   |                  |                   |                   |                |                  |
| Patient must have previously received PBS-subsidised treatment with this drug for this condition,   |                  |                   |                   |                |                  |
| <b>AND</b>  |                  |                   |                   |                |                  |
| <b>Clinical criteria:</b>   |                  |                   |                   |                |                  |
| Patient must have no more than 15% blasts in the bone marrow or peripheral blood that are not attributable to any cause other than AML.           |                  |                   |                   |                |                  |
| <b>AND</b>  |                  |                   |                   |                |                  |

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|---|
| <b>Clinical criteria:</b>   |
| Patient must not be receiving concomitant PBS-subsidised midostaurin.   |
| <b>Administrative Advice:</b> No increase in the maximum quantity or number of units may be authorised.   |
| <b>Administrative Advice:</b> No increase in the maximum number of repeats may be authorised.   |
| <b>Administrative Advice:</b> Special Pricing Arrangements apply.   |
| <b>Caution:</b> Oral azacitidine should not be used interchangeably with injectable azacitidine due to differences in the exposure, dose and schedule of treatment.   |
| <b>Caution:</b> This is a category X drug and must not be given to pregnant women. Pregnancy must be avoided during treatment and for at least 6 months following cessation of therapy.   |
| <b>Administrative Advice:</b> 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 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday). |

| MEDICINAL PRODUCT<br>medicinal product pack  | PBS item<br>code | Max. qty<br>packs | Max. qty<br>units | No. of<br>Rpts | Available brands |
|--|------------------|-------------------|-------------------|----------------|------------------|
| AZACITIDINE  |                  |                   |                   |                |                  |
| azacitidine 300 mg tablet, 7   | NEW              | 3                 | 21                | 1              | Onureg           |
| <b>Category / Program:</b> GENERAL – General Schedule (Code GE)  |                  |                   |                   |                |                  |
| <b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners  |                  |                   |                   |                |                  |
| <b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required ( <i>in writing - legacy</i> ) - Postal/HPOS upload or Online PBS Authorities immediate assessment           |                  |                   |                   |                |                  |
| <b>Condition:</b> Acute Myeloid Leukaemia  |                  |                   |                   |                |                  |
| <b>Indication:</b> Acute Myeloid Leukaemia   |                  |                   |                   |                |                  |
| <b>Treatment Phase:</b> Dose escalation therapy – Continuing treatment   |                  |                   |                   |                |                  |
| <b>Clinical criteria:</b>  |                  |                   |                   |                |                  |
| Patient must have previously received PBS-subsidised treatment with this drug for this condition,  |                  |                   |                   |                |                  |
| <b>AND</b>   |                  |                   |                   |                |                  |
| <b>Clinical criteria:</b>  |                  |                   |                   |                |                  |
| Patient must have 5% to 15% blasts in the peripheral blood or bone marrow, in conjunction with clinical assessment, in order to extend the dose schedule as per the TGA Product Information. |                  |                   |                   |                |                  |
| <b>AND</b>   |                  |                   |                   |                |                  |
| <b>Clinical criteria:</b>  |                  |                   |                   |                |                  |
| Patient must not be receiving concomitant PBS-subsidised midostaurin.  |                  |                   |                   |                |                  |
| <b>Administrative Advice:</b> No increase in the maximum number of repeats may be authorised.  |                  |                   |                   |                |                  |
| <b>Administrative Advice:</b> No increase in the maximum quantity or number of units may be authorised.  |                  |                   |                   |                |                  |
| <b>Administrative Advice:</b> Special Pricing Arrangements apply.  |                  |                   |                   |                |                  |
| <b>Caution:</b> Oral azacitidine should not be used interchangeably with injectable azacitidine due to differences in the exposure, dose and schedule of treatment.                          |                  |                   |                   |                |                  |
| <b>Caution:</b> This is a category X drug and must not be given to pregnant women. Pregnancy must be avoided during treatment and for at least 6 months following cessation of therapy.      |                  |                   |                   |                |                  |

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**Prescribing Instructions:**

*Authority applications must be made via the Online PBS Authorities System (real time assessment), or in writing via HPOS form upload or mail:*

*If the application is submitted through HPOS form upload or mail, it must include:*

- (a) a completed authority prescription form; and*
- (b) a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice)*

**Prescribing Instructions:**

*Authority applications must include:*

- a) details (blast percentage, date, unique identifying number/code or provider number) of the pathology test demonstrating blast percentage*

*All reports must be documented in the patient's medical records.*

**Administrative Advice:**

*Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).,*

*Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at [www.servicesaustralia.gov.au](http://www.servicesaustralia.gov.au),*

*Applications for authorisation under this restriction should be made in real time using the Online PBS Authorities system (see [www.servicesaustralia.gov.au/HPOS](http://www.servicesaustralia.gov.au/HPOS)).*

*Alternatively, applications for authority to prescribe can be submitted online using the form upload facility in Health Professional Online Services (HPOS) at [www.servicesaustralia.gov.au/hpos](http://www.servicesaustralia.gov.au/hpos),*

*Or mailed to:*

*Services Australia  
Complex Drugs  
Reply Paid 9826  
HOBART TAS 7001*

***This restriction may be subject to further review. Should there be any changes made to the restriction the sponsor will be informed.***

## **15 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.

## **16 Sponsor’s Comment**

The Sponsor welcomes the PBAC’s decision to recommend oral azacitidine (Onureg®) for maintenance therapy in certain patients with acute myeloid leukaemia (AML) who are not candidates for, including those who choose not to proceed to, haematopoietic stem cell transplantation (HSCT), and will work with the PBAC and the Department of Health and Aged Care to provide access for these patients in need.

## **17 Corrigendum**

The following changes were made:

| <b>Change made</b>  | <b>Date of revision</b> |
|---|-------------------------|
| Table 19 was updated to include references to the post PBAC correction            | 29 June 2023            |
| Paragraph 11.5 was added to explain the error identified post PBAC                | 29 June 2023            |
| Paragraph 11.9 was added to explain the changes to the financial impact estimates | 29 June 2023            |
| Table 21 was updated to include the post PBAC revised estimates                   | 29 June 2023            |
| Paragraph 11.10 was amended to include the revised total estimates                | 29 June 2023            |
| Paragraph 11.11 was amended to include the revised effective AEMP                 | 29 June 2023            |