One Wales Medicine Assessment Group summary of decision rationale

Medicine: venetoclax (Venclyxto®) with azacitidine
Indication: For the treatment of relapsed/refractory acute myeloid leukaemia in adults following at least one line of intensive chemotherapy before or following allogenic haematopoietic stem cell transplant (HSCT) as an alternative to intensive chemotherapy.

Meeting date: **03 November 2025**

Criteria	OWMAG opinion
Clinical effectiveness	OWMAG were presented with the Evidence Status Report (ESR) and noted the rationale for use of venetoclax with azacitidine for treatment of relapsed or refractory (R/R) acute myeloid leukaemia (AML) as an alternative to intensive chemotherapy. The group noted the current treatments for patients with R/R AML who are ineligible for intensive chemotherapy typically involves low-intensity regimens such as low-dose cytarabine, palliative therapies, or off-label venetoclax in combination with azacitidine. The group acknowledged that there was a risk balance for older or less fit patients where the potential gains with receiving FLAG-Ida may be lower and the toxicity greater. So, whilst FLAG-Ida would be a treatment option, venetoclax with azacitidine would offer a less demanding and less toxic treatment option with the potential to offer curative intent (bridge to hematopoietic stem cell transplant [HSCT]) in some patients. The group also acknowledged that the proposed place of venetoclax with azacitidine would not include patients with targetable FLT3 mutations for whom gilteritinib would be a licensed and NICE-approved treatment option. OWMAG considered the available real-world evidence, including UK-based observational studies by Wood et al. (2022, 2025) and a multicentre Canadian retrospective study by Pelland et al. (2024). Across these studies, venetoclax-based therapy achieved overall response rates of 52–55% and median overall survival of 6.8–8.9 months, with higher responses observed in patients with molecular relapse or minimal residual disease. Bridging to HSCT was achieved in 30-38% of patients and the group recognised that for those unsuitable for HSCT a sustained response may be achieved. The group noted that outcomes with venetoclax and azacitidine were generally less favourable than those achieved with intensive salvage chemotherapy. However, indirect comparisons between venetoclax with azacitidine and FLAG-Ida were not possible due to heterogeneity in study designs and patient characteristics. In particular,

	patients receiving venetoclax were typically older, had higher-risk disease, and were less fit for intensive therapy, making direct comparison problematic. Input from the clinical expert supported the rationale for considering venetoclax with azacitidine as a less intensive alternative for patients less suitable for FLAG-Ida. The group noted the poor adverse event profile associated with intensive chemotherapy compared with the less intensive venetoclax and azacitidine regimen. OWMAG considers that, while direct clinical evidence for venetoclax with azacitidine in R/R AML is limited, the available real-world data suggest potential clinical benefit for selected patients ineligible for intensive therapy.
Cost-effectiveness	There is no published cost effectiveness evidence available for this treatment. Therefore, OWMAG considered the cost consequence analysis (CCA) and an exploratory cost utility analysis (CUA) presented in the ESR. The CCA compared venetoclax with azacitidine versus FLAG-Ida. Costs included in the CCA were medicine acquisition, administration, inpatient stay, adverse events, and subsequent treatment (HSCT). Clinical outcomes focussed on median overall survival and response rate. The incremental cost indicated that venetoclax and azacitidine were cost saving but the incremental median overall survival and incremental median response rate was negative when compared to FLAG-Ida. Sensitivity analyses indicated that the cost results were most sensitive to rate of HSCT between treatments. An additional scenario analysis was conducted by AWTTC to offer further contextualisation of incremental cost and clinical outcomes, applying the cost-utility methodology. The same UK-based utility value was applied to both groups. Utility estimates for adverse events were calculated based on NICE TA765. Results were presented with and without a severity multiplier of 1.7. The results indicated that the treatment was cost effective. The group acknowledged the limitations of the analyses in terms of uncertainty due to heterogeneity of patients both within studies and between studies for both venetoclax with azacitidine and for the FLAG-Ida comparator studies. The costing approach was limited as it excluded palliative care ongoing resource use, donor lymphocyte infusion (DLI) and additional monitoring costs. The group acknowledged that HSCT rates had the most impact on incremental costs. However, the group considered that patients suitable for

	treatment with venetoclax and azacitidine were less likely to be eligible for HSCT than patients who would be suitable for FLAG-Ida and therefore this assumption in difference in uptake rates of HSCT was reasonable. On consideration of these factors OWMAG were unable to definitively conclude a cost effectiveness position for venetoclax with azacitidine. However, the health economic evidence suggested that the incremental cost implication of delivering venetoclax with azacitidine is reasonable in the context of the potential health impact.
Budget impact	OWMAG considers the clinical estimate of patient numbers to be reasonable. The group considers that the clinical assumptions underlying the budget impact estimates are generally reasonable. Differences in baseline patient characteristics between venetoclax with azacitidine and FLAG-Ida cohorts, including prior allogeneic HSCT, number of previous treatments, and overall fitness, have been taken into account. The main driver of the budget impact is the cost of HSCT, with lower rates expected in the venetoclax-treated population. OWMAG notes that variation in treatment cycles, adverse event rates, and additional care needs, including palliative care or hospitalisation for monitoring, introduces uncertainty. Administration costs for venetoclax with azacitidine may be higher in some patients who may be monitored in hospital for tumour lysis syndrome during initiation of therapy. FLAG-Ida costs may be underestimated if G-CSF is required beyond seven days or if patients require more prolonged hospital stay. Costs for further treatments beyond HSCT, consolidation therapies such as DLI, or palliative care have not been fully included. OWMAG considers that, based on the estimated number of eligible patients and the expected treatment pathway, the overall budget impact is likely to be low. The use of venetoclax with azacitidine is expected to provide a bridge to HSCT for some patients ineligible for intensive salvage therapy. The group also noted that venetoclax with azacitidine is currently being accessed for patients in Wales via Individual Patient Funding Requests. OWMAG consider the budget impact to be reasonable value for money for NHS Wales.

Resource use	OWMAG note that treatment with venetoclax with azacitidine typically involves more treatment cycles than intensive salvage chemotherapy such as FLAG-Ida. However, as venetoclax with azacitidine is largely outpatient and lower intensity, the overall resource use for administration and supportive care is likely lower than for intensive chemotherapy. The group note that monitoring for patients on venetoclax with azacitidine may be less intensive overall, although hospitalisation may be required during initiation of therapy to monitor for tumour lysis syndrome in some patients, whereas intensive chemotherapy requires substantial inpatient stay for administration and supportive care. The group considers that any potential additional resource use with venetoclax with azacitidine is acceptable, as it may be offset by lower inpatient requirements and reduced management needs for serious treatment-related adverse events. Venetoclax with azacitidine is likely to be associated with lower resource use for adverse event management than intensive chemotherapy, reflecting lower rates of grade ≥3 toxicities and reduced need for hospital-based interventions.
Other factors	The group understand that the prognosis for patients with relapsed or refractory AML who are ineligible for intensive chemotherapy and lack targetable mutations is poor, and that treatment in this setting is generally expected to be palliative or focused on disease control rather than cure. Patients should be informed of the potential options and that venetoclax with azacitidine may provide lower response rates when compared to FLAG-Ida. The group considered the lay perspective, highlighting the treatment's potential to improve quality of life and reduce travel burden for patients accessing tertiary centres. These factors were acknowledged as important in understanding the broader impact of the recommendation.
Final recommendation	OWMAG recommends the use of venetoclax with azacitidine for the treatment of relapsed/refractory acute myeloid leukaemia in adults following at least one line of intensive chemotherapy before or following allogenic haematopoietic stem cell transplant (HSCT) as an alternative to intensive chemotherapy. This recommendation is subject to the development of appropriate start/stop criteria.

Summary of rationale	Despite limited clinical evidence, OWMAG considers that venetoclax with azacitidine may provide meaningful clinical benefit for selected patients with R/R AML who are ineligible for intensive salvage therapy. The associated cost is viewed as a reasonable use of NHS resources in this context. Real-world data will continue to be captured to further assess the effectiveness and value of this treatment in the NHS Wales setting.