Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2412

# venetoclax 10mg, 50mg and 100mg film-coated tablets (Venclyxto®)

AbbVie

04 March 2022

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

**ADVICE**: following a full submission assessed under the end of life and orphan equivalent medicine process

**venetoclax (Venclyxto ®)** is accepted for use within NHSScotland.

**Indication under review:** in combination with a hypomethylating agent for the treatment of adult patients with newly diagnosed acute myeloid leukaemia (AML) who are ineligible for intensive chemotherapy.

In a phase III study, treatment with venetoclax in combination with azacitidine significantly improved overall survival and remission rate when compared with azacitidine alone.

This advice applies only in the context of an approved NHSScotland Patient Access Scheme (PAS) arrangement delivering the cost-effectiveness results upon which the decision was based, or a PAS/ list price that is equivalent or lower.

This advice takes account of the views from a Patient and Clinician Engagement (PACE) meeting.

**Chairman**
**Scottish Medicines Consortium**

## Indication

In combination with a hypomethylating agent for the treatment of adult patients with newly diagnosed acute myeloid leukaemia (AML) who are ineligible for intensive chemotherapy.[1-3]

## Dosing Information

The recommended venetoclax dosing schedule is 100mg on day one, 200mg on day two and 400mg on day three and beyond. The tablets should be swallowed whole with water, at approximately the same time each day, and taken with a meal in order to avoid a risk for lack of efficacy. The tablets should not be chewed, crushed, or broken before swallowing. [1-3]

During the dose-titration phase, venetoclax should be taken in the morning to facilitate laboratory monitoring.

Azacitidine should be administered at 75mg/$m^2$ either intravenously or subcutaneously on days 1 to 7 of each 28-day cycle beginning on cycle 1 day 1.

Venetoclax dosing may be interrupted as needed for management of haematologic toxicities and blood count recovery.

Venetoclax, in combination with a hypomethylating agent, should be continued until disease progression or unacceptable toxicity is observed.

Treatment with venetoclax should be initiated and supervised by a physician experienced in the use of anticancer medicinal products. For further information, including prevention of tumour lysis syndrome and monitoring, please see the Summary of Product Characteristics.[1-3]

## Product availability date

28 May 2021

Venetoclax meets SMC end of life and orphan equivalent criteria for this indication.

## Summary of evidence on comparative efficacy

Venetoclax is a potent, highly selective, inhibitor of B-cell lymphoma-2 (BCL2), an anti-apoptotic protein that is overexpressed in AML cells where it mediates tumour cell survival and has been associated with resistance to chemotherapies.[1-3]

The key evidence in the indication under review comes from VIALE-A, an international, randomised, double-blind, parallel group, phase III study, which evaluated the efficacy and safety of venetoclax in combination with azacitidine versus azacitidine alone.

This study recruited adult patients with AML who were ineligible for standard induction therapy due to age or co-morbidities. Patients were eligible if they had a projected life expectancy of at least 12 weeks; an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2 for patients ≥75 years of age or of 0 to 3 for patients ≥18 to 74 years of age; and no history of treatment with a hypomethylating agent or favourable risk cytogenetics.[4]

Patients were randomised in a 2:1 ratio to receive in 28 day-cycles venetoclax 400mg orally once daily on days 1 to 28 plus azacitidine 75mg/$m^2$ subcutaneously (SC) or intravenously (IV) (per local

label) daily on days 1 to 7 of each cycle (n=286) or placebo orally once daily on days 1 to 28 plus azacitidine 75mg/m$^2$ SC or IV (per local label) daily on days 1 to 7 of each cycle (n=145). Treatment was to continue until disease progression, unacceptable toxicity or intolerance, until patients withdrew consent, or until they met any protocol-defined criteria for discontinuation. Randomisation was stratified according to age (18 to <75 years and ≥75 years), cytogenetic risk (intermediate risk or poor-risk) and region (US, EU, China, Japan, Rest of world). [4]

The co-primary outcomes were overall survival and the percentage of patients with complete remission (CR) and complete remission with incomplete blood count recovery rate (CRi), CR/CRi, as assessed by investigator. Efficacy analyses were performed in the intention-to-treat population, which included all 431 patients who underwent randomisation. A hierarchical statistical testing strategy was applied in the study for the primary and secondary outcomes with no formal testing of outcomes after the first non-significant outcome in the hierarchy.[4]

Venetoclax plus azacitidine significantly improved overall survival and CR/CRi rate compared with azacitidine.[4, 5] Results for the co-primary outcomes are presented in Table 1.

**Table 1: Co-primary outcomes of VIALE-A. [4, 5]**

| | **Venetoclax plus azacitidine** | **Placebo plus azacitidine** |
|---|---|---|
| **Composite remission rate (complete remission plus complete remission with incomplete blood count recovery) based on investigator assessment** | | |
| Data cut-off date (primary remission analysis) | 1 October 2018 | |
| Number of patients | N=147 | N=79 |
| CR/CRi rate, % | 65% | 25% |
| p-value | <0.001 | |
| Data cut-off date (descriptive analysis) | 4 January 2020 | |
| Number of patients | N=286 | N=145 |
| CR/CRi rate, % | 66% | 28% |
| **Overall survival** | | |
| Data cut-off date (interim analysis 2) | 4 January 2020 | |
| Number of patients | N=286 | N=145 |
| Median duration of follow-up, months | 20.5 | |
| Number of deaths | 161 | 109 |
| Median overall survival, months | 14.7 | 9.6 |
| HR (95% CI) | 0.66 (0.52 to 0.85) | |
| p-value | <0.001 | |
| KM estimate at 6 months | 72% | 64% |
| KM estimate at 12 months | 56% | 44% |
| KM estimate at 24 months | 37% | 18% |

Abbreviations: HR, hazard ratio; CI, confidence interval; KM, Kaplan-Meier; CR/CRi, complete remission and complete remission with incomplete blood count recovery.

The submitting company presented post-hoc subgroup analyses from VIALE-A, including for overall survival for patients with 20% to 30% blast cell count at diagnosis. Results of this analysis indicate no significant differences between venetoclax plus azacitidine and azacitidine in terms of overall survival as the hazard ratio crosses the value of one. However, in this blast-restricted subgroup,

median overall survival was still higher in the venetoclax plus azacitidine group compared with azacitidine group with a similar overall survival gain.[6]

The key secondary outcomes supported the co-primary outcomes. Across the venetoclax plus azacitidine and azacitidine groups, respectively, 43% (124/286) and 7.6% (11/145) of patients achieved CR/CRi by the initiation of cycle 2 (p<0.001). At baseline, transfusion independent rate was defined as having received red blood cells (RBC) and/or having received platelets within 8 weeks prior to study treatment (or prior to randomisation if not dosed). Transfusion independence, defined as a 56-day or greater RBC and platelet transfusion-free period while on study therapy (patients who did not receive study drug were considered transfusion dependent during the study), was evaluated for both groups. In the venetoclax plus azacitidine group, 60% (171/286) patients achieved RBC transfusion independence compared to 35% (51/125) patients in the azacitidine group (p<0.001). In the respective groups, 68% and 50% achieved platelet transfusion independence (p<0.001). Complete remission was defined as an absolute neutrophil count >103/µL, platelets >105/µL, red cell transfusion independence, normal marrow differential with <5% blasts, absence of circulating blasts and blasts with Auer rods and no evidence of extramedullary disease. The CR rate was 37% of venetoclax plus azacitidine and 18% of azacitidine patients (p<0.001).[4,5]

Patient-reported outcomes were assessed (descriptively due to a break in hierarchical testing order) during VIALE-A study as secondary outcomes. The severity of fatigue and its impact were assessed using the Patient-Reported Outcomes Measurement Information System (PROMIS) Cancer Fatigue SF 7a questionnaire, which is a seven-item that assess fatigue over the prior 7 days. General health-related quality of life was assessed using the European Organisation for Research and Treatment of Cancer Quality of life Questionnaire (EORTC QLQ-C30). Overall, there were no differences between the treatment arms in terms of fatigue and other patient-reported outcomes.[5]

The submitting company conducted a series of propensity score weighting (PSW) analyses using individual patient data from VIALE-A, VIALE-C[8] and the Haematological Malignancy Research Network database (HMRN).[9] The outcomes assessed included overall survival and event-free survival (EFS), and CR and CRi for the comparison of VIALE-A and VIALE-C only. A Bayesian network meta-analysis (NMA) was also conducted to compare the efficacy of venetoclax in combination with azacitidine (VIALE-A study) versus low-dose cytarabine (AZA-AML-001[7]), in patients with a blast cell count of at least 30%. The outcomes assessed included overall survival and composite remission rate. The submitting company concluded that results of the PSW and NMA analyses indicate that venetoclax plus azacitidine is more effective than low-dose cytarabine (in the >30% blasts subgroup) in reducing the risk of death and improving CR/CRi and EFS time in patients with untreated AML. The company decided to use a naïve indirect comparison of VIALE-A and VIALE-C for the low dose cytarabine comparison in the economic case to maximise the available sample size as the results were similar to the PSW analyses.

*Other data were also assessed but remain confidential.**

## Summary of evidence on comparative safety

Overall, the safety profile of venetoclax plus a hypomethylating agent was consistent with the established safety profiles of the agents and natural history of AML. The risks associated with the treatment are manageable through medical management with routine clinical assessment.[5]

In the VIALE-A study at data cut-off 04 January 2020, the median duration of treatment in the venetoclax plus azacitidine group was 7.6 months and in the azacitidine group was 4.3 months. All patients experienced at least one treatment-emergent adverse event. In the venetoclax plus azacitidine (N=283) and azacitidine (N=144) groups respectively, patients reporting a grade 3 or higher AE were 99% versus 97%, patients with a reported serious AE were 83% versus 73%, patients with a dose reduction due to treatment-emergent AEs were 2.5% versus 4.2%, the proportion of AEs that led to dose interruptions were 53% versus 28% and patients discontinuing therapy due to an AE was 24% versus 20%.[4, 5]

The most frequently reported treatment-emergent AEs of any grade with an incidence >20% in the venetoclax plus azacitidine group versus the azacitidine group were: thrombocytopenia (46% versus 40%), nausea (44% versus 35%), constipation (43% versus 39%), neutropenia (42% versus 29%), febrile neutropenia (42% versus 19%), diarrhoea (41% versus 33%), vomiting (30% versus 23%), hypokalaemia (29% versus 28%), anaemia (28% versus 21%), decreased appetite (25% versus 17%), peripheral oedema (24% versus 18%), pyrexia (23% versus 22%), pneumonia (23% versus 27%), leukopenia (21% versus 14%) and fatigue (21% versus 17%).[4] A similar proportion of patients in each group had a treatment-related adverse event that led to death (23% in the venetoclax plus azacitidine group versus 20% in the azacitidine group).[5]

## Summary of clinical effectiveness issues

Acute myeloid leukaemia (AML) is an aggressive type of cancer of the myeloid line of blood cells. It is characterised by an excess production of immature myeloid blood cells in the bone marrow, which do not go on to become mature blood cells and prevent the normal production of blood cells. AML primarily affects older adults, with a rising incidence in patients over 60 years and a median age at diagnosis of 68 years.[4, 5] Treatment options for AML include intensive induction chemotherapy followed by consolidation chemotherapy, allogeneic stem cell transplantation, or both; however, not all patients diagnosed are eligible for treatment with intensive chemotherapy due to advanced age, coexisting conditions, and a high incidence of unfavourable genomic features. Instead, the main treatment options for these patients include less intensive regimens with hypomethylating agents such as azacitidine or decitabine, and low-dose cytarabine.[5] Only azacitidine has been accepted by SMC for use for treatment of adult patients who are not eligible for haematopoietic stem cell transplantation with AML with 20–30% blasts and multilineage dysplasia (SMC589/09) (in the absence of a submission from the holder of the marketing authorisation, azacitidine was not recommended for use within NHSScotland in patients with >30% marrow blasts [SMC1175/16]). Venetoclax meets SMC end of life and orphan equivalent

criteria for this indication. Clinical experts consulted by SMC considered that venetoclax plus azacitidine fills an unmet need in this therapeutic area.

In VIALE-A, treatment with venetoclax plus azacitidine was associated (at the second interim analysis) with a statistically significant and clinically meaningful improvement in overall survival with a median gain of 5.1 months over azacitidine alone. In addition, at the primary remission analysis, venetoclax plus azacitidine was associated with a significantly increased CR/CRi remission rate versus azacitidine alone (65% versus 25%, respectively). A descriptive analysis at the second interim analysis of overall survival showed similar remission rate results. [4, 5]

A hierarchical testing order was used for primary and secondary outcomes. The majority of secondary outcomes showed significant benefits with venetoclax plus azacitidine; however, there was a break near the end of the hierarchical testing order (overall survival in the FLT3 subgroup did not show significant benefit with venetoclax plus azacitidine); thus, the patient reported outcomes (which were to be tested last in the hierarchical order) were not formally compared.[4, 5]

Patients with prior treatment with a hypomethylating agent and a favourable risk cytogenetics (such as t(8;21), inv(16), t(16;16) or t(15;17)) were not eligible for VIALE-A study, thus it is uncertain if results can be extrapolated to these patients. In addition, the European Medicines Agency noted that although CR/CRi was improved across AML genomic risk groups and an increased overall survival was seen in some of the subgroups (most notably among patients with either de novo or secondary AML, intermediate cytogenetic risk, and IDH1 or IDH2 mutations), these results should be interpreted with caution due the small size of these subgroups.[5]

Venetoclax was licensed in combination with any hypomethylating agent. However, only data in combination with azacitidine was presented to support the clinical case. The efficacy and safety of venetoclax in combination with other hypomethylating agents remains uncertain and the clinical case of any other combination was not made.

The submitting company described as relevant comparators: azacitidine in patients with blast count between 20 and 30%, and low-dose cytarabine in patients with blast count >30%. Thus, they conducted subgroup analyses of VIALE-A in these relevant blast-restricted subgroups; these analyses, although relevant, were only conducted post-hoc and their results should be interpreted with caution.

There is no direct evidence comparing venetoclax in combination with a hypomethylating agent against low-dose cytarabine. Thus, the submitting company presented PSW and NMA analyses. A number of limitations affect the validity of these analyses, including small sample size and limited outcomes compared. Despite these limitations, the company's conclusions seem reasonable.

Clinical experts consulted by SMC considered that venetoclax in combination with a hypomethylating agent is a therapeutic advancement in the treatment of the indication under review. They suggested that in-patient admission for the first few days of treatment may be needed, which is not the case with treatments currently used in the indication under review.

## Patient and clinician engagement (PACE)

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of venetoclax, as an orphan-equivalent and end of life medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- AML is a rapidly progressing and life-threatening haematological malignancy. Its diagnosis is devastating for patients and their families and carers. Patients experience distressing symptoms (such as fatigue, pain and depression); and there are negative emotional and financial impacts on patients and their families and carers.

- Patients who are ineligible for intensive chemotherapy (often the elderly and less fit) have a very poor outlook. Their condition is incurable and there are very few treatment options with limited efficacy. Thus, there is a high unmet need in this setting.

- Venetoclax in combination with azacitidine could help address this need by providing an additional treatment option, which would reduce AML morbidity and mortality and could be used for all patients ineligible for intensive chemotherapy.

- This combination is expected to lead to increased remission rates, with more rapid and durable response than existing options. In responders, it is expected to increase survival and disease control, reducing symptoms and reliance on transfusion (thus reducing hospital visits). This would hugely improve the patient's wellbeing and help maintain independence for longer. Patients may be able to continue to participate in work, education and family activities (including caring for family members), and their quality of life could be restored.

- The expected benefits need to be balanced against higher rates of infectious and bleeding complications, the need for in-patient admission and more frequent monitoring during the first cycle of treatment due to tumour lysis syndrome risk. Although this treatment leads to increased infectious risk, this risk already exists with current options. After the first cycle of treatment, this combination is generally well tolerated.

- Clinicians already have experience of using this combination in specific subgroups of AML.

**Additional Patient and Carer Involvement**

We received a patient group submission from Leukaemia Care which is a registered charity. Leukaemia Care has received 14.3% pharmaceutical company funding in the past two years, including from the submitting company. Representatives from Leukaemia Care participated in the PACE meeting. The key points of their submission have been included in the full PACE statement considered by SMC.

## Summary of comparative health economic evidence

The submitting company provided lifetime cost-utility analyses for venetoclax in combination with azacitidine for the treatment of adult patients with newly diagnosed AML who are ineligible for intensive chemotherapy. Separate analyses were presented for patients with 20-30% blasts and >30% blasts given the use of different comparator therapies in each group. The comparators were azacitidine and low-dose cytarabine respectively.

Patients enter the model in either a remission or non-remission state. This reflects an instant application of composite remission (complete or incomplete) based on relevant clinical data. Patients are then at risk of progressive disease or relapse (combined state), and death. A fifth state of 'cure' is also modelled. This is possible only for people treated with venetoclax plus azacitidine, as comparator therapies are considered by the submitting company not to be associated with the deep remission that it argues can be considered to represent cure. Cure is deemed to be achieved by all patients treated with venetoclax plus azacitidine who remain in remission at two years, and is associated with general population life expectancy, without future possibility of relapse. Two-year remission following incomplete count recovery is included as cure as this can reportedly be a direct result of the myelosuppressive nature of the treatment combination in some patients.

The model is populated with clinical data from VIALE-A for the 20-30% blasts analysis and an unadjusted comparison of VIALE-A and C for the >30% blasts analysis. The model then applies hazard functions for progression or relapse, and mortality (from remission, non-remission, and progressive or relapsed disease). The relevant transitions are distinct from the primary endpoint in the clinical studies and the submitting company acknowledged that the fit of these functions is affected by small effective sample sizes. Selection of distributions was performed applying criteria of statistical and visual assessment of goodness of fit, and clinical opinion. Given the relatively small sample sizes, limited follow up, and the impact of censoring, there is uncertainty in the non-parametric hazards with often little apparent basis for preference of one distribution compared to others. Estimates of treatment effects are not applied as independent functions and are fitted and applied for each arm in the model (based on the individual patient data from VIALE-A and the population adjusted indicted comparisons). In addition to being independently fitted, transitions are informed by different distributions in each arm in some cases. This can lead to situations where hazards are assumed to decrease in one arm, while increasing in the other, without there being clear empirical evidence for this based on the limited available data. The impact this has on the analysis may, however, be limited given the central feature of the cure assumption in the model.

The submitting company refers to remission as being 'correlated' with improved survival, with the rate of relapse after two years being low, and refers to a 'plateau' in the Kaplan-Meier at 24 months. Evidence of cure, however, is uncertain. While the expectation of better long-term outcomes for patients who achieve a two-year remission may be uncontentious, the model assumes no risk of relapse after two years. The submitting company does acknowledge some uncertainty and includes a scenario option whereby a higher standardised mortality ratio is applied.

Adverse event rates (Grade 3/4) are included in the model. Other than for neutropenia and febrile neutropenia, there were few differences between venetoclax plus azacitidine and comparators.

Health related quality of life is incorporated in the analyses based on pooled (i.e. across arms) EQ-5D-5L scores cross-walked to EQ-5D-3L utility index (van Hout et al, 2012[10]). A linear mixed-effects (LMM) regression model was developed with independent variables reflecting health state status (event free survival with CR/CRi, event free survival without CR/CRi, progressive disease or relapse). Pre-treatment EQ-5D were incorporated as reference, with random effects analysis to account.

The dosing schedule for venetoclax plus azacitidine was 400mg venetoclax orally once daily following induction on days 1-3 with 100mg, 200mg, and 400mg, and azacitidine at 75mg/$m^2$ (body surface area) on days 1-7 of each 28 day treatment cycle. For azacitidine as comparator the dose schedule was as above, and for low-dose cytarabine 20mg per $m^2$ on each of days 1-10 of each treatment cycle. According to the submitting company, many patients require dose reductions due to side effects, use of strong/moderate CYP3A inhibitors, and requirements for treatment interruptions. In the base case analysis, dose intensity estimates for azacitidine and low-dose cytarabine were based on the post-hoc analyses of VIALE-A and VIALE-C trial data, validated by clinical experts as being reflective of dose intensities seen in UK clinical practice. The dose intensity of the venetoclax component was based on the submitting company's clinical experts' opinions as clinicians indicated that the dose intensity for the venetoclax component in VIALE-A was higher than expected, and a dose intensity of 50% was applied. The company cites an American Society of Haematology abstract[11] reporting no dose-response relationship associated with venetoclax dose reductions when CYP3A inhibitors are prescribed concomitantly, based on analysis of VIALE-A and therefore clinical outcomes were not adjusted for dose adjustments.

Health state resource use included outpatient and emergency department visits, diagnostic procedures and tests, blood transfusion, and hospitalisations. In the model people treated with azacitidine or low-dose cytarabine in the first line are assumed not to receive subsequent gilteritinib after discontinuation, whereas a small proportion of patients receiving for venetoclax plus azacitidine are eligible for subsequent treatment with gilteritinib (due to response leaving them fitter following treatment and better able to receive subsequent gilteritinib). However, only patients who are positive for FLT3 mutations can be considered for treatment with gilteritinib. Therefore, in the base case analysis 3% of patients receive gilteritinib after receiving venetoclax plus azacitidine, with all remaining patients receiving hydroxycarbamide. Patients receiving azacitidine or low-dose cytarabine all go on to receive hydroxycarbamide.

Accounting for proportions treated with gilteritinib and hydroxycarbamide the mean per cycle cost following discontinuation of venetoclax plus azacitidine is £563. This contrasts with £137 in each of the comparator arms (100% hydroxycarbamide). Scenario analyses consider greater use of gilteritinib in the venetoclax plus azacitidine (5%) and azacitidine (3%) arms.

A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a discount was offered on the list price.

The base case results and key sensitivity analyses are presented in the tables below.

**Table 2: Base-case Cost per QALY results at venetoclax PAS price**

| | **Incremental cost effectiveness ratio (ICER)** |
|---|---|
| **Venetoclax plus azacitidine versus azacitidine- 20-30% blasts population** | £16,743 |
| **Venetoclax plus azacitidine versus low-dose cytarabine- >30% blasts population** | £34,296 |

Sensitivity analyses indicated in both blasts analyses that the ICER was most sensitive to treatment costs, the cure state utility estimate, proportion in remission at model initiation, and alternative discounting scenarios. Scenario analyses were also presented. The range of alternative distributions were considered individually. None of these alternative scenarios in terms of distributions had any substantial impact on the ICER in either comparison. Assuming cure occurs later than two years did have an impact on the ICER, as did setting the venetoclax plus azacitidine dose adjustment to the level reported in VIALE-A.

**Table 3: Scenario analyses**

| | | **ICER (cost/QALY)** | |
|---|---|---|---|
| | | **20-30% blasts** | **>30% blasts** |
| | | **versus azacitidine** | **versus low-dose cytarabine** |
| | **Base Case** | **£16,743** | **£34,296** |
| 1 | 2.5-year cure point | £27,247 | £41,574 |
| 2 | 3-year cure point | £38,789 | £49,691 |
| 3 | 60% DI for venetoclax | £19,209 | £36,292 |
| 4 | Patients in cure health state have same utility as patients in remission health state | £16,758 | £34,324 |
| 5 | Alternative assumption regarding use of gilteritinib; greater use of gilteritinib in the venetoclax plus azacitidine (5%) and azacitidine (3%) arms | £16,115 | £35,137 |
| 6 | 10-year model time horizon | £19,608 | £43,177 |
| 7 | SMR of 1.2 applied to patients in the cure health state | £17,675 | £34,296 |

Abbreviations: DI, dose intensity; ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life year; SMR, standardised mortality ratio.

There are a number of limitations:

- As shown in scenarios 1, 2 and 7 in the table above, venetoclax plus azacitidine's cost-effectiveness is sensitive to assumptions around cure, for which evidence is limited. Following the New Drugs Committee meeting, the submitting company provided some additional analysis varying the proportion of patients on venetoclax plus azacitidine who move from the remission state at 2 years to the cure state (assumed 100% in the base case). If 20% of these patients remain in remission rather than moving to the cure state, the ICERs increased to £25,114 in the 20-30% blast population and £44,855 in the >30% blasts group.
- While necessary to allow for the different comparators of relevance to the cost-effectiveness case, patients are assigned to remission on entry to the model on the basis of post hoc sub-group analyses, without statistical evidence of sub-group effects. In the case of the >30% blasts group, these data were taken from an unadjusted comparison of VIALE-A and VIALE-C.
- There is uncertainty in the analysis of transition rates due to small effective sample sizes, as the submitting company acknowledges. However extensive sensitivity analyses were provided to test alternative approaches and as noted above, the ICERs did not rise considerably.
- There were some lesser concerns regarding the valuation of health related quality of life, assignment of mortality risk, and accumulation of costs in the cure state may be optimistic.

The Committee also considered the benefits of venetoclax in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that the criterion for a substantial improvement in life expectancy in the patient population targeted in the submission was satisfied. In addition, as venetoclax is an orphan equivalent medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence, the output from the PACE process, and after application of the appropriate SMC modifiers, the Committee accepted venetoclax for use in NHSScotland.

*Other data were also assessed but remain confidential.**

## Additional information: guidelines and protocols

The European Society for Medical Oncology (ESMO) published guidance titled "Acute myeloblastic leukaemias in adult patients: ESMO clinical practice guidelines for diagnosis, treatment and follow-up" in March 2020. For patients with newly diagnosed AML who are not eligible for intensive chemotherapy, these guidelines recommend azacitidine and decitabine as the first choice of treatment. Use of venetoclax in combination with azacitidine, decitabine or low-dose cytarabine is mentioned as a treatment available in the United States and Israel. However, at the time the publication, their approval was pending in the European Union.[12]

The European LeukaemiaNet (ELN) consensus guidance Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel was published in November 2016. For patients within the indication under review, these guidelines recommend

azacitidine, decitabine, low-dose cytarabine and best supportive care (including hydroxyurea; for patients who cannot tolerate any antileukemic therapy, or who do not wish any therapy).[13]

## Additional information: comparators

Azacitidine or low-dose cytarabine.

## Additional information: list price of medicine under review

| Medicine | Dose Regimen | Cost per year (£) |
|---|---|---|
| **venetoclax** | **orally once daily: 100mg on day 1, 200mg on day 2 and 400mg on day 3 and beyond** | **Year 1: 62,049**<br>**Year 2 onwards: 62,263** |

*Costs from BNF online on 30 November 2021. Costs do not take patient access schemes into consideration.*

## Additional information: budget impact

The company estimated there would be 63 patients eligible for treatment with venetoclax plus azacitidine per year. The uptake rate was estimated to be 18% of eligible patients in year 1 rising to 50% thereafter. This resulted in 11 patients estimated to receive treatment in year 1 rising to 32 in subsequent years.

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS.

*Other data were also assessed but remain confidential.**

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This assessment is based on data submitted by the applicant company up to and including 10 January 2022.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/About_SMC/Policy*

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

**Advice context:**

*No part of this advice may be used without the whole of the advice being quoted in full.*

*This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.*