SMC2533

azacitidine film-coated tablets (Onureg®)

Bristol Myers Squibb Pharmaceuticals Ltd

09 June 2023

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

azacitidine (Onureg®) is accepted for use within NHSScotland.

Indication Under Review: maintenance therapy in adult patients with acute myeloid leukaemia who achieved complete remission or complete remission with incomplete blood count recovery following induction therapy with or without consolidation treatment and who are not candidates for, including those who choose not to proceed to, haematopoietic stem cell transplantation.

Oral azacitidine plus best supportive care resulted in statistically significant improvements in overall survival and relapse-free survival, when compared with placebo plus best supportive care.

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.

Chair
Scottish Medicines Consortium

1. Clinical Context

1.1. Medicine background

Azacitidine is a pyrimidine nucleoside analogue that inhibits tumour cell growth by reducing deoxyribonucleic acid (DNA), ribonucleic acid (RNA) and protein synthesis; and inhibits tumour growth through DNA-methylation (hypomethylation).[1, 2] Onureg® is the first licensed oral formulation of azacitidine, and has no other licensed indications.[1] A subcutaneous formulation of azacitidine is also licensed, and has been accepted by SMC for the treatment of adult patients who are not eligible for haematopoietic stem cell transplant (HSCT) with intermediate-2 and high-risk myelodysplastic syndrome (MDS), chronic myelomonocytic leukaemia (CMML) or acute myeloid leukaemia (AML) (SMC589/09). However, the oral and subcutaneous formulations of azacitidine are not considered bioequivalent.[1, 3]

The recommended dose of oral azacitidine is 300mg once daily for days 1 to 14 of every 28-day treatment cycle. Patients who experience an AML relapse, with 5% to 15% blasts in the peripheral blood or bone marrow, in conjunction with a clinical assessment, can receive an extended dosing schedule from days 14 to 21 of each 28-day treatment cycle. Treatment should be continued until no more than 15% of blasts are observed in peripheral blood or bone marrow or until unacceptable toxicity. Please see the summary of product characteristics (SPC), link is available in section 9.3, for further information.[1]

1.2. Disease background

AML is an aggressive and rapidly progressing cancer that is characterised by an excess production of immature myeloid blood cells (blasts) in the bone marrow, which do not go on to become mature blood cells and prevent the normal production of blood cells.[2, 4] AML predominantly affects older people, with a rising incidence in patients over 60 years and a median age at diagnosis of 68 years.[5] In Scotland, in patients over 60 years old, the five-year average incidence of AML is approximately 121 patients per year;[6] five-year survival rates are 13% and 18%, for men and women in Scotland, respectively.[7]

1.3. Treatment pathway and relevant comparators

The standard treatment for newly diagnosed AML, for patients who can tolerate it, is intensive induction chemotherapy, which can induce complete remission (CR) in 40% to 60% of patients over 60 years old;[8] however, 80% to 90% of these patients will relapse without further treatment.[9] Post-remission options include consolidation therapy for which there is no international consensus for the optimum number of cycles. However, patients will have a reduced relapse risk with more consolidation cycles;[2, 3] and ESMO guidelines recommend at least 2 consolidation cycles in CR patients not undergoing HSCT.[10] For patients with intermediate or high-risk disease who achieve CR or CR with incomplete blood count recovery (CRi), HSCT represents the best chance of cure.[11, 12] However, HSCT is not a feasible option for all patients, with the number of patients undergoing HSCT decreasing with increasing age due to coexisting conditions, poor organ function, and limited donor availability.[2, 8, 13] For patients who are not candidates for HSCT, current salvage therapy options at the time of relapse are inadequate, and maintenance therapy is not established practice since studies have only shown improvements in relapse free-survival (RFS), and not in overall survival, after standard intensive chemotherapy (for example with subcutaneous azacitidine).[2, 8]

SMC has accepted the use of midostaurin as a maintenance treatment for newly diagnosed AML patients (SMC 1330/18). However, this is only for patients who are FMS-like tyrosine kinase 3 (FLT3) mutation-positive, who are in complete response following treatment with standard daunorubicin and cytarabine induction and high-dose cytarabine consolidation chemotherapy; this does not include patients with a CRi or who have undergone HSCT. ESMO guidelines recommend up to three consolidation cycles should be administered to FLT3-mutated patients who do not undergo HSCT.[10]

1.4. Category for decision-making process

Eligibility for a PACE meeting

Oral azacitidine meets end of life and orphan equivalent criteria.

2. Summary of Clinical Evidence

2.1. Evidence for the licensed indication under review

Evidence to support the efficacy and safety of oral azacitidine comes from the QUAZAR AML-001 study. Details are summarised in Table 2.1.

Table 2.1. Overview of relevant studies

Criteria	QUAZAR AML-001 study[2, 8]
Study Design	An international, randomised, double-blind, placebo-controlled, phase III study.
Eligible Patients	• Patients aged ≥55 years of age, with an ECOG PS of 0 to 3. • Newly diagnosed, histologically confirmed *de novo* acute AML[a] or AML secondary to MDS or CMML. • Have recovered from induction chemotherapy (that is intensive chemotherapy), with or without consolidation therapy) with adequate bone marrow function (ANC ≥0.5 x 10^9/L and platelet count ≥20 x 10^9/L). • Achieved first CR or CRi status (criteria include <5% of blasts in bone marrow) within 4 months (±7 days) prior to randomisation. • No prior bone marrow transplantation or HSCT, and were not candidates for HSCT at screening.[b] • Had not achieved CR/CRi following treatment with hypomethylating agents.
Treatments	• Oral azacitidine 300mg or matching placebo once daily on days 1 to 14 of repeated 28-day cycles. • Remission status was assessed (by bone marrow and peripheral blood examinations) at cycles 3, 6, 9, 12, 15, 18, 21, 24, 30, 36, and as clinically indicated thereafter. • Treatment continued until AML relapse (>15% blasts in the peripheral blood or bone marrow) that was attributable to relapse following CR/CRi and not any other cause (for example bone marrow regeneration following consolidation therapy). • Patients who had an AML relapse with 5% to 15% blasts in the peripheral blood or bone marrow were permitted to have their dosing regimen increased to 21 days at the discretion of the investigator. • All patients could receive best supportive care, which included blood product transfusions, erythropoiesis-stimulating agents, granulocyte colony-stimulating factors, nutritional support, and antibiotic, antiviral, antifungal, antiemetic, or antidiarrheal therapies.

Randomisa-tion	Patients were randomised equally and stratified according to age at time of induction therapy (55 to 64 years versus ≥65 years), prior history of MDS or CMML (yes versus no), cytogenetic risk category at time of induction therapy (intermediate versus poor), and receipt of consolidation therapy following induction (yes versus no).
Primary outcome	The primary outcome was overall survival, which was assessed in all randomised patients. Data was censored for patients: lost to follow-up, who were alive at the end of follow-up, and who withdrew consent.
Secondary outcomes	RFS, defined as the time from the date of randomisation to the date of documented relapse or death, whichever occurred first. Documented relapse was defined as the earliest date of any of the following: ≥5% BM blasts from the central pathology report; the appearance of >0% blasts in the peripheral blood with a later BM confirmation (BM blasts ≥5%) within 100 days; or at least two peripheral blasts ≥5% within 30 days.
Statistical analysis	A hierarchical statistical testing strategy was applied in the study with no formal testing of outcomes after the first non-significant outcome in the hierarchy. The order of the hierarchical statistical testing analysis was overall survival, then RFS.

[a]defined as AML without an antecedent hematologic disorder
[b]there were no trial-specified criteria associated with transplantation eligibility.

AML = acute myeloid leukaemia; ANC = absolute neutrophil count; BM = bone marrow; BSC = best supportive care; CMML = Chronic myelomonocytic leukaemia; CR = complete remission; CRi = complete remission with incomplete blood count recovery; ECOG PS = Eastern Cooperative Oncology Group Performance Status; HSCT = haematopoietic stem cell transplant; MDS = myelodysplastic syndromes; RFS = relapse free survival

At the primary analysis (data cut-off 15 July 2019), oral azacitidine resulted in statistically significant improvements in overall survival and RFS when compared with placebo (see table 2.2 for detailed results).[2, 8] After the primary analysis, patients who demonstrated clinical benefit from receiving oral azacitidine were permitted to enter the unblinded extension phase of the study, where they could continue to receive oral azacitidine; patients on placebo discontinued treatment and crossover was not permitted in the extension phase.[14, 15] Upon trial unblinding, 16% (39/238) of patients in the oral azacitidine group continued into the extension phase. Updated results from the extension phase for overall survival (data cut-off 08 September 2020; median follow-up of 51.7 months) are supportive of the overall survival results from the earlier data cut-off (15 July 2019).[14]

The submitting company also provided evidence from the European subgroup in the QUAZAR AML-001 study and considered this to be the most generalisable population to Scottish clinical practice; this subgroup consisted of 67% (314/472) of the intention to treat (ITT) population.[2] Results for overall survival (data cut-off 08 September 2020 only) and RFS (data cut-off 15 July 2019 only) were directionally consistent, though more favourable, with those in the ITT population. These results from the European subgroup have been used to inform the base case for the cost-effectiveness analysis; the ITT population have been included as a supportive analysis.

Table 2.2. Primary and selected secondary outcomes from the QUAZAR AML-001 study.

	ITT population	
Data cut-off date	15 July 2019[2, 8]	
	Oral azacitidine (n=238)	**Placebo (n=234)**
Median follow-up	41.2 months	
Primary outcome: overall survival		
Deaths, n	158	171
HR (95% CI), p-value	0.69 (0.55 to 0.86), p<0.001	
Median overall survival (months)	24.7	14.8
KM estimated overall survival at 24 months	51%	37%
KM estimated overall survival at 36 months[a]	37%	28%
Secondary outcome: Relapse-Free Survival (RFS)[b]		
RFS Events, n	164	181
HR (95% CI), p-value	0.65 (0.52 to 0.81), p<0.001	
Median RFS (months)	10.2	4.8
KM estimated RFS at 24 months	27%	17%

[a] from 08 September 2020 cut-off.

[b] The submitting company advised that data for RFS was not collected at the 08 September 2020 cut-off, as this relied on data from the extension phase, where bone marrow and peripheral blood samples were not routinely collected; these results would be deemed unreliable as a result.[2] Therefore, the RFS data presented for the ITT population and the European subgroup is from the 15 July 2019 cut-off only.
Abbreviations: CI = confidence interval, HR = hazard ratio; ITT = intention to treat; KM = Kaplan-Meier CI = confidence interval, HR = hazard ratio, ITT = intention-to-treat, KM = Kaplan-Meier

The submitting company also provided post-hoc analysis data from the proportion of patients in the ITT population who had an FLT3 mutation at diagnosis (n=66). In the oral azacitidine group and placebo groups respectively, median overall survival was 28.2 months and 9.7 months in those with an FLT3 mutation; and 24.7 months and 15.2 months in those without an FLT3 mutation.[16] The improvements in RFS for oral azacitidine compared with placebo were increased in patients with a FLT3 mutation (median RFS: 23.1 months versus 4.6 months), compared to patients without an FLT3 mutation (median RFS: 10.2 months versus 4.9 months). These results for overall survival and RFS are consistent with those seen with the ITT population.

2.2. Health-related quality of life outcomes

Health-related quality of life (HRQoL) was assessed using the Functional assessment of chronic illness therapy-fatigue scale (FACIT – fatigue scale) and the European Quality of Life-Five dimensions-Three levels (EQ-5D-3L) health utility index and visual analogue scale; these scales were analysed as change from baseline and the proportion of patients with clinically meaningful improvement based on a prespecified minimally important difference. HRQoL scores on the FACIT-fatigue scale and EQ-5D-3L improved over time in both groups; these improvements were similar in both groups, with no clinically meaningful deterioration over time.[1, 2, 8]

2.3. Indirect evidence to support clinical and cost-effectiveness comparisons

The submitting company, based on clinical experts they contacted, claim that most patients with an FLT3 mutation would undergo HSCT. It is estimated that FLT3 mutations occur in 25% to 30% of AML cases,[2] and 30% to 40% of these patients will achieve first remission; this would result in an estimated 10% of patients within the licensed indication likely to have midostaurin treatment in Scotland. Experts contacted by SMC suggest that these estimates appear to be reasonable. In the absence of direct head-to-head evidence comparing oral azacitidine with midostaurin (a relevant comparator for patients who have an FLT3 mutation and are in CR), the submitting company presented an indirect treatment comparison, as described in Table 2.3. The submitting company concluded that oral azacitidine was associated with improvements in overall survival and RFS, when compared to midostaurin. However, the results and the conduct of the ITC make this conclusion from the submitting company very uncertain (see section 4.2 for more details).

Table 2.3: Summary of indirect treatment comparison

Criteria	Overview
Design	Anchored Bucher indirect treatment comparison using a fixed-effect model. Due to the differences in eligibility criteria of the two trials, individual patient data were matched to only include patients with FLT3-mutation positive AML in complete remission. However, the company decided against using the hazard ratios from the Bucher ITC and instead conducted time-varying methods to identify the best fitting survival model for use in the economics.
Population	Adult patients with FLT3 mutation-positive AML, who were in complete remission.
Comparators	Midostaurin (50mg twice daily) in combination with standard daunorubicin and cytarabine induction chemotherapy (up to two cycles), and high-dose cytarabine consolidation chemotherapy (four 28-day cycles).
Studies included	Two studies: QUAZAR AML-001 study (FLT3-mutation-positive sub-group only)[8] and the RATIFY study (trial population who in CR who entered the maintenance phase only).[17]
Outcomes	Overall survival and RFS; these outcomes were used for the economic analysis. However, RFS was not assessed in the RATIFY study, the submitting company considered the outcomes event-free survival (EFS) and disease-free survival (DFS) to be synonymous with RFS, for the purpose of this ITC.
Results	In the indirect comparisons before and after matching, hazard ratios for overall survival and RFS crossed one, suggesting no evidence of difference between treatments.

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

3. Summary of Safety Evidence

The overall safety profile of oral azacitidine was considered manageable, acceptable, and was consistent with the known safety profile of parenteral azacitidine.[2]

In the QUAZAR AML-001 study at data cut-off 15 July 2019, the median duration of treatment in the oral azacitidine group was 11.6 months (range: 0.5 to 74.3 months) and in the placebo group was 5.7 months (range: 0.7 to 68.5 months). A regulatory authority deemed the lower exposure of the placebo group to be related to the earlier relapse of the disease.[2]

In the oral azacitidine (n=236) and placebo (n=233) groups respectively, patients reporting a grade 3 or higher adverse event (AE) were 72% versus 63%, patients with a reported serious AE were 34% versus 25%, patients with a dose reduction due to treatment emergent AEs were 16% versus 2.6%, the proportion of AEs that led to dose interruptions were 43% versus 17% and patients discontinuing therapy due to an AE was 13% versus 4.3%.[2, 8]

The most frequently reported treatment-emergent AEs of any grade (incidence ≥20% in either treatment group), in the oral azacitidine group versus the placebo group were: nausea (65% versus 24%), vomiting (60% versus 10%), diarrhoea (50% versus 21%), neutropenia (44% versus 26%), constipation (39% versus 24%), thrombocytopenia (33% versus 27%), fatigue (30% versus 19%), anaemia (20% versus 18%).[2, 8]

Haematologic AEs (neutropenia, thrombocytopenia, and anaemia) and infections occurred more frequently in the oral azacitidine group compared to placebo; though these were largely managed with dose interruptions and dose reductions. Febrile neutropenia was the most common serious AE (7.0% versus 4.0%), the SPC advises that Granulocyte Colony-Stimulating Factor (G-CSF) and anti-infective medications should be considered during oral azacitidine treatment as prophylaxis for the treatment of neutropenia and infections.[1, 2]

A regulatory authority highlighted that the high incidence of gastrointestinal toxicities raises concerns about patient compliance outside of the trial setting.[2], therefore anti-emetic medication is advised before each dose of oral azacitidine for at least the first two treatment cycles.[1]

4. Summary of Clinical Effectiveness Considerations

4.1. Key strengths

- In the QUAZAR AML-001 study, oral azacitidine resulted in a statistically significant improvement in median overall survival of 9.9 months (after a median follow-up of 41.2 months) in the ITT population, when compared with placebo; this was considered clinically meaningful.[2, 3]
- Oral azacitidine also resulted in a statistically significant improvement in median RFS of 5.4 months, when compared with placebo.[2, 3]
- The overall safety profile of oral azacitidine was considered manageable, acceptable, and was consistent with the known safety profile of parenteral azacitidine.[2]

4.2. Key uncertainties

- The choice to use the European subgroup from the QUAZAR AML-001 study, rather than the full ITT population, for the base case in the economic analysis is questionable. The reasons the submitting company gave were they considered the characteristics of the European subgroup to be more generalisable to Scottish clinical practice than the ITT population, and that there may be differences in how AML is managed in the rest of the world compared to Europe. However, a regulatory authority concluded that the overall study results can be applied to the global population and not only to the European population; meaning that the potential clinical benefit from oral azacitidine treatment would be expected in both the ITT and European

populations.[2] In addition, there are uncertainties around subgroup analyses, the risk of results being due to chance and the need for caution when interpreting these. Therefore, the use of the ITT population for the base case in the economic analysis may be more appropriate.

- From the ITT population, many patients only received one (45%) or zero (20%) consolidation cycles before randomisation. Firstly, this may have resulted in a selection bias that could have exaggerated the observed treatment effect of oral azacitidine over placebo in an undertreated population.[3] Secondly, patients will have a reduced relapse risk with more consolidation cycles,[2, 3] and ESMO guidelines recommend at least 2 consolidation cycles in CR patients not undergoing HSCT.[10] Additionally, experts contacted by SMC advised that they recommend at least two cycles of consolidation therapy for patients ineligible for HSCT. The low number of patients who received more than one cycle of consolidation therapy potentially limits the generalisability of the results to the Scottish setting.

- Patients who were in CR or CRi after induction therapy were included in the study but there was no specific requirement for patients to be in CR or CRi at the point of randomisation, prior to the start of study treatment. Additionally, randomisation to oral azacitidine was not stratified by post-induction response, which may have resulted in more patients in the placebo group (4.7%) not achieving either CR or CRi status at randomisation compared with the oral azacitidine group (2.1%). Since, it is recognised that patients with AML who do not achieve CR after intensive induction therapy have poorer overall survival and RFS compared to those who do, then this could have had a negative impact on both outcomes in the placebo group.[3, 18, 19]

- In the oral azacitidine and placebo groups respectively, 6.3% and 14% of patients received subsequent salvage and curative HSCT after study drug discontinuation; it is unclear if these patients would experience improved survival benefit.[8] Overall survival sensitivity analyses, which censored patients who received any subsequent AML treatments, showed an overall survival hazard ratio that is consistent with the ITT population; which indicates that the overall survival of these 10% of patients would likely be lower if they never received their subsequent HSCT.[2]

- There were several limitations with the ITC providing indirect comparative evidence for oral azacitidine versus midostaurin in the subpopulation with an FLT3 mutation (potentially accounting for 10% of patients eligible for oral azacitidine), which substantially affected its validity and robustness. Based on statistician feedback, the assumptions made by the company, and the decision not to use the hazard ratios from their anchored Bucher analysis were unjustified. There were also significant differences between the study designs (for example the secondary outcome in QUAZAR AML-001 was RFS whilst it was disease free and event free survival in the RATIFY study), and patient characteristics (for example in QUAZAR AML-001 patients were over 55 years; in RATIFY they were 18 to 59 years). Experts contacted by SMC expected the uptake of oral azacitidine in the FLT3 mutation positive patients to be low, with midostaurin the preferred option.

4.3. Clinical expert input

Clinical experts consulted by SMC considered that oral azacitidine fills an unmet need in this therapeutic area, and is a therapeutic advancement, since there are no maintenance treatments

available for most patients within this indication that have shown significant improvements in overall survival after standard intensive chemotherapy. Clinical experts consulted by SMC considered that the place of therapy for oral azacitidine would be as per the indication under review.

4.4. Service implications

Clinical experts consulted by SMC considered that the introduction of this medicine would result in these patients requiring more clinic visits to review their oral medicine. However, it was not felt that this would be significant since the patient numbers are small and there will be no day unit requirements.

5. 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 **azacitidine (Onureg®),** 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 an aggressive cancer that is usually diagnosed at a point where patients are already suffering with a significant symptom burden. Without treatment, it is life-threatening and whilst HSCT remains the most effective treatment option for AML, it is not suitable for many patients with AML due to several factors; additionally many patients choose not to receive HSCT due to the associated risks of significant morbidity and mortality.
- There are no established maintenance treatments for most patients with AML, who are ineligible for, or choose not to have, HSCT; though a small proportion of AML patients with an FLT3 mutation have the option of maintenance therapy with midostaurin. The risk of relapse for all AML patients without HSCT is extremely high, and is most likely to occur in the first year after reaching remission with induction and/or consolidation chemotherapy.
- Based on the QUAZAR AML-001 study, oral azacitidine is a maintenance treatment that could prolong the time to relapse and survival following induction and/or consolidation chemotherapy. It has a tolerable side effect profile, and is not associated with any clinically meaningful deterioration in health-related quality of life assessments.
- Given the lack of treatment options, and with many of these patients feeling 'forgotten' about, oral azacitidine would offer a maintenance treatment option that could have significant positive psychosocial and financial implications for this group of patients and their families. A patient group representative shared the views of AML patients, some of whom have received parenteral azacitidine, which concur with this assessment.
- This is an oral medicine, which would allow patients to take their treatment at home and spend more time at home with their families and friends. It appears to be tolerable and is associated with less hospitalisations than placebo (current standard of care for most patients with AML after completing intensive therapy); therefore, this would reduce the need for families and/or carers to attend hospital for treatment-related toxicities, and would reduce the

care needs of the patient at home.

- The introduction of oral azacitidine would likely have a minimal service impact since it is an oral medicine that is administered at the patient's home. Despite the use of oral azacitidine meaning an increase in the number of treatments they would need to take, AML patients would be willing to try additional treatments if it could prevent relapse.

Additional Patient and Carer Involvement

- We received a patient group submission from Leukaemia Care, which is a registered charity. Leukaemia Care has received 27% pharmaceutical company funding in the past two years, with none from the submitting company. A representative 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.

6. Summary of Comparative Health Economic Evidence

6.1. Economic case

The submitting company provided an economic case as described in Table 6.1.

Table 6.1 Description of economic analysis

Criteria	Overview
Analysis type	Cost-utility analysis
Time horizon	Life time (30 years)
Population	AML patients who achieved CR or CRi following induction therapy and who are not candidates for HSCT. This was matched to the product licence.
Comparators	Watch and wait, which comprised of no active treatment. Analysis was also provided comparing oral azacitidine against midostaurin in the FLT3 mutation population.
Model description	The company utilised a three state partitioned survival model. Those three states were relapse free (RF), relapsed disease (RD) and death. The model did not include a HSCT state. Patients undergoing HSCT were attributed a one off cost and utility adjustment and modelled as remaining in the RD state.
Clinical data	Clinical evidence on overall survival and RFS within the model came from the European cohort of the QUAZAR AML-001 study.[2, 8] An indirect treatment comparison was conducted for the comparison with midostaurin. Patient level data from the ITT population of the QUAZAR AML-001 study was matched to the inclusion criteria of the RATIFY study.[17] The overall survival and RFS Kaplan Meier data from the RATIFY study were digitised to be used in extrapolation analysis.
Extrapolation	Survival curves were fitted to patient level data. In the central analysis jointly fitted log-logistic curves were used to extrapolate RFS. Jointly fitted generalised gamma curves were used to extrapolate overall survival. No treatment waning or cure rate were assumed in the base case. In the FLT3 subgroup analysis, the company selected individually fitted one-knot odds linear models to extrapolate RFS. Individually fitted generalised gamma models were used to extrapolate overall survival.
Quality of life	EQ-5D data from QUAZAR AML-001 were used to estimate the utility of the RF state. Utility was assumed equal for all patients in the RF state, regardless of treatment arm or treatment status. The utility value of someone in the RD state was based on a utility decrement derived from Joshi et al (2019) applied to the RF state value.[20] HSCT surgery was associated with a one off disutility, which lasted for 28 days and represented the immediate negative health impact of the surgery. After that patients who had received HSCT were assumed to have the same utility value as those in the RD state.

Costs and resource use	Medicine costs covered the acquisition and administration costs of oral azacitidine as well as the AE costs of those receiving both oral azacitidine and watch and wait. Second line treatment costs were also included. Wider costs consisted of haematologist visits, nurse visits, lab tests, chemistry and liver panels, RBC transfusions, platelet transfusions and bone marrow aspirate/biopsies. One off costs were applied in the case of HSCT and end of life.
PAS	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. The results presented for the FLT3 subgroup do not take account of the PAS for midostaurin but these were considered in the results used for decision-making. SMC is unable to present the results provided by the company which used an estimate of the PAS price for midostaurin due to commercial confidentiality and competition law issues.

6.2. Results

The base case analysis, in the full licence population and inclusive of the relevant PAS discounts, indicated that oral azacitidine led to an increase in costs but also an increase in health outcomes. The projected increase in costs were primarily through medicine acquisition costs, administration costs and disease management costs. The estimated quality-adjusted life-year (QALY) gains in the oral azacitidine arm were from increased time spent in the RF state. The incremental cost effectiveness ratio (ICER) was estimated at £41,236.

The results from the analysis of the FLT3 sub-population, which included the PAS discount on oral azacitidine but not midostaurin, suggested that oral azacitidine could be described as dominant. That means that oral azacitidine was predicted to generate lower costs and higher health outcomes than midostaurin.

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

6.3. Sensitivity analyses

To explore uncertainty, the company provided a variety of sensitivity analyses. Those sensitivity analyses suggested that results for the full licence population were most responsive to changes in the utility values, relative dose intensity and treatment administration costs.

Uncertainty was further explored through scenario analysis. A selection of the scenarios generated are provided in Table 6.3. These scenarios present results for the full licence population and include the PAS discount on oral azacitidine.

Table 6.3: Scenario analysis (Full licence population) - PAS discount applied to oral azacitidine

#	Scenario description	Base case description	ICER (£/QALY)
Time horizon scenarios			
1	Time horizon: 15 years	Time horizon: 30 years	42,641
2	Time horizon: 20 years		41,626
Survival model: Extrapolation OS			
3	Joint log-normal	Joint generalised gamma model	40,668
4	Joint log-logistic		40,827
5	Individual generalised gamma		41,837
Survival model: Extrapolation RFS			
6	Joint log-normal	Joint log-logistic model	41,897
7	Individual log-logistic		41,833

Survival model: Extrapolation of oral azacitidine time on treatment			
8	Generalised gamma	Weibull	44,931
Cure assumption			
9	Include 5-year cure point (OS only)	No cure point	40,160
Treatment waning			
10	Treatment waning from Month 90	No treatment waning	41,294
11	Treatment waning from Month 36		41,927
QUAZAR AML-001 study population			
12	ITT population	European population	48,549
Utility values			
13	Joshi et al (2019)[20]	RF: QUAZAR AML-001, RD: adapted from Joshi (2019)	38,356
14	Tremblay et al. (2018)[21]		41,861

Abbreviations: AE: adverse event; HSCT: haematopoietic stem cell transplant; ICER: incremental cost effectiveness ratio; LY: life year; OS: overall survival; QALY: quality adjusted life year; RFS: relapse-free survival.

6.4. Key strengths

The key strengths of the analysis are:

- The central comparator of watch and wait was appropriate, matching current practice in Scotland.
- The primary economic analysis was informed by a large head-to-head study.

6.5. Key uncertainties

The key uncertainties of the analysis are:

- The company chose to use the European cohort of the QUAZAR AML-001 study to inform the main economic analysis, arguing that it was the most representative of Scottish patients. However, as outlined in the clinical section, the appropriateness of that choice was uncertain and scenario analysis using that ITT population led to an increase in the ICER (see Scenario 12).
- The modelling extrapolated OS and RFS beyond the observation period of the QUAZAR-AML01 study, introducing uncertainty into the economic results. However, the company reported following best practice guidance and having received some clinical feedback in selecting the base case assumptions. Alternative parametric survival curves which appeared to correspond with the evidence provided by the company showed relatively modest variation in the ICER value (see scenarios 3 to 7).
- The company presented a comparison between oral azacitidine and midostaurin within the FLT3 subgroup. This was reliant upon an indirect treatment comparison, which was seen as highly uncertain based on the heterogeneity between the studies and the methodological approach used. Those results should be viewed with caution, although based on clinical feedback the uptake of oral azacitidine in the FLT3 population was expected to be low.

7. Conclusion

The Committee considered the benefits of oral azacitidine 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 oral azacitidine is an orphan medicine, SMC can accept greater uncertainty in the economic case.

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

8. Guidelines and Protocols

European Society for Medical Oncology (ESMO) published in 2020: Acute myeloid leukaemia in adult patients: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up.[10]

European LeukaemiaNet (ELN) published recommendations in 2022: Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN.[9]

9. Additional Information

9.1. Product availability date

October 2022

9.2. Summary of product characteristics

See the SPC for further information such as dosing (including the extended dosing schedule) and safety. Available from: azacitidine 200mg or 300mg film-coated tablets (Onureg®).

Table 9.1 List price of medicine under review

Medicine	Dose regimen	Cost per year (£)
Azacitidine film-coated tablets	**Of a 28-day treatment cycle:** **300mg once daily for days 1 to 14** **Treatment should continue until >15% blasts are observed in the peripheral blood or bone marrow.**	**152,542**

Costs from eMC Dictionary of Medicines and Devices Browser on 14 March 2023. Costs do not take any patient access schemes into consideration.

10. Company Estimate of Eligible Population and Estimated Budget Impact

The submitting company estimated there would be 14 patients eligible for treatment with azacitidine in each year. Accounting for uptake and discontinuation, the company estimated that 1 patient would receive treatment in year 1 rising to 8 patients in year 5.

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. This template does not incorporate any PAS discounts associated with comparator medicines or PAS associated with medicines used in a combination regimen.

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

References

1. Bristol Myers Squibb Pharmaceutical Ltd. Azacitidine 200mg and 300mg film-coated tablets (Onureg®). Summary of product charateristics. Electronic Medicines Compendium www.medicines.org.uk/emc/ Last updated 26 Oct 2022.
2. European Medicines Agency (EMA). European Public Assessment Report. Oral azacitdine (Onureg®). EMEA/H/C/004761/0000. Published: 22 April 2021. Available at: https://www.ema.europa.eu/en/documents/assessment-report/onureg-epar-public-assessment-report_en.pdf [Accessed: 02 September 2022].
3. United States Food and Drug Administration (FDA). New Drug Application (NDA) Multidisciplinary Review and Evaluation of oral azacitidine (Onureg®) – Application Number: 214120. Published: 01 September 2020. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/214120Orig1s000MultidisciplineR.pdf [Accessed: 06 March 2023].
4. National Cancer Institute. Acute Myeloid Leukaemia Treatment. Last updated: 18 January 2023. Available at https://www.cancer.gov/types/leukemia/hp/adult-aml-treatment-pdq [Accessed: 19 January 2023].
5. DiNardo CD, Jonas BA, Pullarkat V, Thirman MJ, Garcia JS, Wei AH, et al. Azacitidine and Venetoclax in Previously Untreated Acute Myeloid Leukemia. N Engl J Med. 2020; 383(7): 617-629.
6. Public Health Scotland. Cancer incidence and prevalence in Scotland to Decemebr 2019 - Leukaemia data sheet. Published: May 2021. Available from: https://publichealthscotland.scot/publications/cancer-incidence-in-scotland/cancer-incidence-in-scotland-cancer-incidence-and-prevalence-in-scotland-to-december-2019/ [Accessed: 07 March 2023].
7. West of Scotland Cancer Network. Audit Report: Acute Leukaemia - Quality Performance Indicators. Available from: https://www.woscan.scot.nhs.uk/wp-content/uploads/Final-Leukaemia-QPI-MCN-Audit-Report-v1.1-22-June-2021.pdf. [Accessed 22 July 2022].
8. Wei AH, Döhner H, Pocock C, Montesinos P, Afanasyev B, Dombret H, et al. Oral Azacitidine Maintenance Therapy for Acute Myeloid Leukemia in First Remission. N Engl J Med 2020; 383: 2526-2537.
9. Döhner H, Wei AH, Appelbaum FR, Craddock C, DiNardo CD, Dombret H, et al. Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN. Blood. 2022 Sep 22; 140(12): 1345-1377.
10. Heuser M, Ofran Y, Boissel N, Brunet Mauri S, Craddock C, Janssen J, et al. Acute myeloid leukaemia in adult patients: European Society for Medical Oncology (ESMO) Clinical Practice Guidelines for diagnosis, treatment, and follow-up. Ann Oncol. 2020 Jun; 31(6): 697-712.
11. Medinger M, Lengerke C, Passweg J. Novel therapeutic options in Acute Myeloid Leukemia. Leuk Res Rep. 2016:6:39-49.
12. Rautenberg C, Germing U, Haas R, Kobbe G, Schroeder T. Relapse of Acute Myeloid Leukemia after Allogeneic Stem Cell Transplantation: Prevention, Detection, and Treatment. Int J Mol Sci. 2019;20(1):228.
13. Bertoli S, Tavitian S, Huynh A, Borel C, Guenounou S, Luquet I, et al. Improved outcome for AML patients over the years 2000-2014. Blood Cancer J. 2017; 7(12): 635.
14. Wei AH, Döhner H, Sayar H, Ravandi F, Montesinos P, Dombret 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. Blood. 2021; 138 (Supplement 1): 871.
15. Bristol Myers Squibb Pharmaceutical Ltd. Data on file: CC-486-AML-001 (QUAZAR) Clinical Study Report. 2020.

16. Döhner H, Wei AH, Roboz GJ, Montesinos P, Thol FR, Ravandi F, et al. Prognostic impact of NPM1 and FLT3 mutations in patients with AML in first remission treated with oral azacitidine. Blood. 2022 Oct 13;140(15):1674-1685.
17. Larson RA, Mandrekar SJ, Huebner LJ, Sanford BL, Laumann K, Geyer S, et al. Midostaurin reduces relapse in FLT3-mutant acute myeloid leukemia: the Alliance CALGB 10603/RATIFY trial. Leukemia. 2021;35(9):2539-2551. .
18. Ovlisen AK, A Oest, MD Bendtsen, J Baech, P Johansen, LS Lynggaard, et al. Stringent or nonstringent complete remission and prognosis in acute myeloid leukmia: a Danish population-base study. Blood Adv. 2018; 2(5): 559-564.
19. Walter RB, Kantarjian HM, Huang X, Pierce SA, Sun Z, Gundacker HM, et al. Effect on complete remission and less than complete remission on survival in acute myeloid leukemia: a combined Eastern Cooperative Oncology Group, Southwest Oncology Group, and M. D. Anderson Cancer Center Study. J Clin Oncol. 2010; 28:1766-1771.
20. Joshi N, Hensen M, Patel S, Xu W, Lasch K, Stolk E. Health State Utilities for Acute Myeloid Leukaemia: A Time Trade-off Study. Pharmacoeconomics. 2019;37(1):85-92.
21. Tremblay G, Dolph M, Patel S, Brandt P, Forsythe A. Cost-effectiveness analysis for midostaurin versus standard of care in acute myeloid leukemia in the United Kingdom. Cost Eff Resour Alloc. 2018;16:33.

This assessment is based on data submitted by the applicant company up to and including 24 May 2023.

**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:*https://www.scottishmedicines.org.uk/about-us/policies-publications/

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.