NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Final appraisal determination

Azacitidine for the treatment of myelodysplastic syndromes, chronic myelomonocytic leukaemia and acute myeloid leukaemia

This guidance was developed using the single technology appraisal (STA) process.

1 Guidance

1.1 Azacitidine is not recommended as a treatment option for people who have the following conditions and are not eligible for haematopoietic stem cell transplantation:

- intermediate-2 and high-risk myelodysplastic syndromes according to the International Prognostic Scoring System (IPSS)
- chronic myelomonocytic leukaemia with 10–29% marrow blasts without myeloproliferative disorder or
- acute myeloid leukaemia with 20–30% blasts and multilineage dysplasia, according to the World Health Organization classification.

1.2 People with the conditions stated in section 1.1 who are currently receiving azacitidine for myelodysplastic syndromes, chronic myelomonocytic leukaemia or acute myeloid leukaemia should have the option to continue treatment until they and their clinicians consider it appropriate to stop.
2 The technology

2.1 Azacitidine (Vidaza, Celgene) is an anticancer drug that is thought to work by re-establishing cells’ natural mechanisms to control abnormal growth. Azacitidine has a UK marketing authorisation for the treatment of adult patients are not eligible for haematopoietic stem cell transplantation with:

- intermediate-2 and high-risk myelodysplastic syndromes according to the International Prognostic Scoring System (IPSS)
- chronic myelomonocytic leukaemia with 10–29% marrow blasts without myeloproliferative disorder or
- acute myeloid leukaemia with 20–30% blasts and multilineage dysplasia, according to World Health Organization classification.

2.2 Azacitidine is contraindicated in patients who have known hypersensitivity to azacitidine or to any of its excipients; in women who are breastfeeding; and in patients with advanced malignant hepatic tumours. The summary of product characteristics (SPC) states that complete blood counts should be performed before starting therapy, and as often as needed, to monitor response and toxicity. The SPC lists precautions for use in patients with liver or kidney impairment, and cardiac or pulmonary disease. The SPC reports that the most common adverse reactions are thrombocytopenia, neutropenia, leukopenia, nausea, vomiting and injection site reactions. For full details of side effects and contraindications, see the SPC.

2.3 Azacitidine is injected subcutaneously daily for 7 days, followed by a rest period of 21 days. The SPC states that patients should be treated for a minimum of six cycles. The recommended dose is 75 mg/m² of body surface area. The SPC states that patients
should be pre-medicated with anti-emetics to prevent nausea and vomiting. The cost of azacitidine is £321 for a 100-mg vial (excluding VAT; ‘British national formulary’ [BNF] edition 58). Based on a body surface area of 1.7 m² and a dose of 75 mg/m², nine vials would be required for one cycle. Costs may vary in different settings because of negotiated procurement discounts.

2.4 The manufacturer has agreed a patient access scheme with the Department of Health, in which azacitidine for the treatment of myelodysplastic syndromes, chronic myelomonocytic leukaemia and acute myeloid leukaemia will be available with a 7% reduction in the acquisition cost. The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS.

3 The manufacturer’s submission

The Appraisal Committee (appendix A) considered evidence submitted by the manufacturer of azacitidine and a review of this submission by the Evidence Review Group (ERG; appendix B) and the Decision Support Unit (DSU; appendix B).

3.1 The main evidence for the efficacy of azacitidine in patients with higher-risk myelodysplastic syndromes, chronic myelomonocytic leukaemia or acute myeloid leukaemia in the manufacturer’s submission was obtained from a phase III, open-label, multicentre, randomised controlled trial (AZA-001; n = 358). Supplementary data from the open-label extension trial of AZA-001 were also provided. In this trial, patients were randomised to receive either azacitidine or a conventional care regimen. Before randomisation, patients were preselected for treatment with one of three conventional care regimens: best supportive care alone, low-dose
chemotherapy (plus best supportive care) or standard-dose chemotherapy (plus best supportive care). Patients receiving a particular conventional care regimen were compared with patients who had been preselected for the same care regimen but were then randomised to treatment with azacitidine. The manufacturer reported that patients randomised to either azacitidine or one of the conventional care regimens were comparable in terms of age, baseline severity of myelodysplastic syndrome, Eastern Cooperative Oncology Group (ECOG) performance status and time since original diagnosis. Randomisation and subsequent analyses were stratified according to the French–American–British classification (FAB) subtype and IPSS group. Of the 179 patients receiving a conventional care regimen, 105 were preselected for best supportive care alone, 49 for low-dose chemotherapy and 25 for standard-dose chemotherapy.

3.2 The primary endpoint in AZA-001 was overall survival. Secondary endpoints included time to transformation to acute myeloid leukaemia, haematological response, independence from red blood cell transfusions for 56 consecutive days or more, number of infections needing intravenous antibiotics and occurrence of adverse events.

3.3 The manufacturer’s submission states that the intention-to-treat median overall survival was 24.5 months for patients receiving azacitidine compared with 15.0 months for patients receiving conventional care regimens ($p = 0.0001$, hazard ratio 0.58, 95% confidence interval [CI] 0.43 to 0.77). The median time to transformation to acute myeloid leukaemia was 17.8 months (interquartile range 8.6 to 36.8, 95% CI 13.6 to 23.6) with azacitidine compared with 11.5 months (interquartile range 4.9 to 11.5).
not reached, 95% CI 8.3 to 14.5) with conventional care regimens (p < 0.0001, hazard ratio 0.50, 95% CI 0.35 to 0.70). The manufacturer reported results within each of the pre-randomisation stratification groups (best supportive care alone, low-dose chemotherapy plus best supportive care, and standard-dose chemotherapy plus best supportive care). Treatment with azacitidine led to statistically significant improvements in overall survival in all stratification groups, except for patients preselected for standard-dose chemotherapy. Only patients preselected for best supportive care demonstrated statistically significant improvement in time to transformation to acute myeloid leukaemia. Of the patients who were dependent on red blood cell transfusions at baseline, 45% of patients treated with azacitidine became transfusion independent during treatment compared with 11.8% of patients receiving conventional care regimens (p < 0.0001). The manufacturer reported that in a subgroup analysis of patients with the –7/del(7q) chromosomal abnormality, median overall survival was higher in patients receiving azacitidine than in those receiving conventional care regimens.

3.4 The ERG considered the results from the AZA-001 trial to be robust and to indicate clinical benefit for patients treated with azacitidine. The ERG noted that the open-label design of the study meant that the results could be subject to bias and that there was an imbalance in the numbers lost to follow-up. This means that the effectiveness in clinical practice could be lower than that observed in AZA-001. In addition, the ERG noted that the results for the comparison with chemotherapy were less robust because of the small numbers of patients included.
3.5 The manufacturer developed an economic evaluation, comprising a two-arm health-state transition model. One arm estimated the costs and outcomes associated with treatment with azacitidine; the other arm estimated the costs and outcomes associated with treatment with the conventional care regimens in the AZA-001 trial (see section 3.1). All modelled patients entered the model in the myelodysplastic syndromes health state at the start of treatment and left the model at death, irrespective of the treatment regimen. The model used a 35-day cycle with a lifetime horizon.

3.6 The manufacturer’s economic model used data from the AZA-001 trial and its extension to estimate effectiveness. The economic model underwent a number of iterations after clarification requests from the Committee, the ERG and the DSU. The manufacturer’s final base-case analysis used a lognormal parametric function to extrapolate the overall survival observed in the trial. Survival data from a myelodysplastic syndromes registry in Düsseldorf were presented in support of the selection of the lognormal function. Sensitivity analyses explored the use of alternative parametric functions. Time to progression was modelled in such a way that progression to the acute myeloid leukaemia health state occurred eight cycles before death to reflect the mean length of time patients had acute myeloid leukaemia in the AZA-001 trial.

3.7 The manufacturer reported that no usable utility data were collected in the AZA-001 trial. Utility estimates for patients treated with azacitidine were taken from the prospective, open-label, multicentre randomised controlled trial CALGB 9221 (n = 191). In this trial, patients with myelodysplastic syndromes were treated with either azacitidine or best supportive care, and European Organisation for Research and Treatment of Cancer (EORTC) quality of life data
were collected. This trial was excluded from the clinical-effectiveness analysis because the patient population was of a lower IPSS risk category than the population specified in the marketing authorisation for azacitidine. The manufacturer converted the EORTC quality of life data into EQ-5D values using an algorithm developed using data from patients with oesophageal cancer. Utility estimates for patients treated with chemotherapy were taken from a publication reporting scores for patients receiving low-dose and standard-dose chemotherapy.

3.8 The manufacturer reported that, when possible, healthcare resource use was determined from AZA-001 protocol regimens. When data were not available from the trial, resource use estimates were based on expert opinion obtained through a questionnaire. Drug costs were taken from the BNF (edition 57). The majority of treatment costs were determined using the NHS 2009/10 tariff. Personal and Social Services Research Unit costs and NHS reference costs (2006/07) were used for resources if a tariff cost was not available. Because azacitidine requires a 7-day continuous treatment cycle, the additional cost of weekend administration was modelled as a two-fold increase in administration cost for 2 days of each treatment cycle. The manufacturer estimated that vial sharing (made possible by treating multiple patients on the same day) could occur for 49% of patients. The reduction in unused vial content resulting from vial sharing was explored in a scenario analysis.

3.9 The manufacturer’s final base-case results (see section 3.6) gave incremental cost-effectiveness ratios (ICERs) for treatment with azacitidine of £47,432 per quality-adjusted life year (QALY) gained for patients in the best supportive care group, £40,754 per QALY gained for patients in the low-dose chemotherapy group, and
£37,105 for patients in the standard-dose chemotherapy group. The scenario analysis that explored vial sharing decreased the base-case ICERs to £44,440, £37,929 and £34,366 per QALY gained for the best supportive care, low-dose chemotherapy and standard-dose chemotherapy groups respectively. Incorporating the patient access scheme reduced the base-case ICERs (and those with vial sharing) to £45,538 (£42,756), £38,966 (£36,399) and £35,371 (£32,823) per QALY gained for the best supportive care, low-dose chemotherapy and standard-dose chemotherapy groups respectively.

3.10 The manufacturer provided cost-effectiveness analyses for each of the parametric survival functions explored. The ICERs referred to below incorporate the patient access scheme. For the analyses using the Weibull survival function, the ICERs were £63,177 per QALY gained for the best supportive care group, £49,030 per QALY gained for the low-dose chemotherapy group, and £51,252 per QALY gained for the standard-dose chemotherapy group. For the analyses using the exponential survival function, the ICERs were £67,203 per QALY gained for the best supportive care group, £58,418 per QALY gained for the low-dose chemotherapy group, and £60,097 per QALY gained for the standard-dose chemotherapy group. For the analyses using the log-normal survival function, the ICERs were £45,538 per QALY gained for the best supportive care group, £38,996 per QALY gained for the low-dose chemotherapy group, and £35,371 per QALY gained for the standard-dose chemotherapy group. For analyses using the baseline survival from the Düsseldorf registry data and applying the respective hazard ratios associated with treatment, the ICERs were £71,522 per QALY gained for the best supportive care group, £58,282 per
QALY gained for the low-dose chemotherapy group, and £85,790 per QALY gained for the standard-dose chemotherapy group.

3.11 The ERG expressed concerns about the different treatment effects seen in the pre-randomisation stratification groups in the AZA-001 trial. It noted that two of the groups, particularly the standard-dose chemotherapy group, consisted of very small numbers of patients, and that to consider the arms of the trial in isolation effectively breaks randomisation.

3.12 The ERG raised concerns about the parametric function selected to model overall survival. It noted that the selection of the lognormal function was not strongly supported by evidence from the AZA-001 trial or its extension, or the Düsseldorf registry data. The ERG reported that when various parametric functions were compared with the individual patient data from the Düsseldorf registry, an exponential survival function underestimated long-term survival, while log-logistic and lognormal survival functions overestimated long-term survival. The ERG noted that the use of log-logistic and lognormal functions estimated a percentage of patients would survive into their nineties, which the ERG considered unrealistic, given the nature of the condition. The ERG reported that of the functions explored, the Weibull survival function provided the best fit to the Düsseldorf registry data. The ERG also reported that when the lognormal survival function was used, the results were not consistent with those of the CALGB 9221 trial, which included a patient population of a lower IPSS risk category than the AZA-001 trial.

3.13 The ERG commented that the time to transformation to acute myeloid leukaemia in AZA-001 was subject to considerable
censoring from loss of patients to follow-up. It therefore considered that the modelled time to transformation was subject to uncertainty.

3.14 The ERG noted several issues with the conversion of EORTC quality of life data into utility scores. The ERG reported that the algorithm used to derive the utility scores was considered by its developers to be less reliable for patients in more severe health states than alternative algorithms that were explored and rejected by the manufacturer. The ERG noted that this could bias the results. It also reported that the algorithm had been developed using data from patients with oesophageal cancer, and that patients eligible for azacitidine were of a similar age to these patients. However, the underlying conditions and comorbidities were potentially very different. The ERG stated that the utility values resulting from the algorithm should be treated with caution.

3.15 In the final iteration of the economic model, the manufacturer explored the impact of adjusting the utility values to account for the differences in the baseline patient characteristics. These were shown to have little impact on the ICERs.

3.16 Full details of all the evidence are in the manufacturer’s submission and the ERG report, which are available from www.nice.org.uk/TAXXX

4 Consideration of the evidence

4.1 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of azacitidine, having considered evidence on the nature of myelodysplastic syndromes, chronic myelomonocytic leukaemia and acute myeloid leukaemia and the value placed on the benefits of azacitidine by patients with the
conditions, those who represent them, and clinical specialists. It also took into account the effective use of NHS resources.

Clinical effectiveness

4.2 The Committee considered the clinical-effectiveness evidence presented by the manufacturer from the pivotal AZA-001 trial. The Committee understood that patients were preselected for treatment with one of the conventional care regimens before randomisation, and this was based on age, ECOG performance status and the presence of comorbidities. It also understood that patients randomised to treatment with azacitidine were stratified according to their pre-randomisation regimen. The Committee heard from the clinical specialists that this group of patients usually receive best supportive care in routine clinical practice in the UK, and that only a small percentage of patients are able to tolerate chemotherapy. The Committee also heard from the clinical specialists that the proportion of patients in each stratification group broadly represented the treatment patients with these conditions receive in the UK (that is, treatment with chemotherapy plus best supportive care is appropriate for considerably fewer patients than treatment with best supportive care alone). However, the Committee also noted survey data provided by the manufacturer from 11 haematologists on the proportion of patients currently treated with each of the comparative care regimens. These data showed pronounced variation in treatment patterns, which indicated that there is no nationally recognised standard of care for this patient population, particularly regarding patients’ eligibility for chemotherapy. Furthermore, the Committee heard from the clinical specialists that most patients who receive chemotherapy in the UK go on to receive stem cell transplantation and are therefore not
eligible to receive azacitidine. Taking all these issues into account, the Committee concluded that best supportive care alone was the most appropriate comparator, as it was received by the majority of patients in the UK.

4.3 The Committee noted that the median overall survival for patients receiving azacitidine was longer than for those receiving the conventional care regimens. The Committee further noted that median time to transformation to acute myeloid leukaemia and the percentage of patients becoming independent of blood transfusions were longer for patients receiving azacitidine than for those receiving the conventional care regimens. The Committee noted that when outcomes were analysed by stratification group, the difference in overall survival between the treatment arms in the standard-dose chemotherapy stratification group was not statistically significant, nor were the differences between the treatment arms in the estimates of time to transformation to acute myeloid leukaemia in the low-dose and standard-dose chemotherapy groups. The Committee was aware that the small patient numbers limited the precision of the outcome estimates by stratification group, but concluded that the estimates of total overall survival appeared robust. The Committee noted that the problems relating to loss of patients to follow-up, as described by the ERG (see section 3.13), may have introduced bias into estimates of relative effectiveness, but concluded that this effect was likely to be minimal.

4.4 The patient experts stated that treatment with azacitidine was associated with relief from fatigue, fewer hospitalisations because of infections, decreased need for blood and platelet transfusion, and increased ability to perform normal activities of daily living. The
Committee heard from the clinical specialists that common adverse events include peripheral blood cytopenias, myelosuppression, nausea, vomiting and injection site reactions. The patient experts and clinical specialists agreed that these adverse events are generally well tolerated. The Committee noted that no quality of life data were collected in the AZA-001 trial, although EORTC data collected in CALGB 9221 suggested improvements in overall health with azacitidine.

4.5 The Committee concluded on the basis of the clinical-effectiveness evidence and the evidence from the clinical specialists and patient experts that azacitidine is a clinically effective treatment for myelodysplastic syndromes, chronic myelomonocytic leukaemia and acute myeloid leukaemia.

Cost effectiveness

4.6 The Committee considered evidence on the cost effectiveness of azacitidine for the treatment of myelodysplastic syndromes, chronic myelomonocytic leukaemia and acute myeloid leukaemia. The Committee was aware of the inconsistency and variation in clinical practice about determining patient eligibility for chemotherapy and that most patients who receive chemotherapy in the UK go on to receive stem cell transplantation and are therefore not eligible to receive azacitidine (see section 4.2). The Committee considered that best supportive care alone was therefore the most appropriate comparator for the economic modelling. It also noted that no cost-effectiveness evidence was presented for the subgroup of patients with the –7/del(7q) chromosomal abnormality.

4.7 The Committee discussed the likelihood of vial sharing. It noted that because of the small number of patients, it may be difficult to
implement a vial-sharing scheme efficiently, and that the estimate of 49% of patients being able to receive treatment at the same time seemed optimistic. The Committee concluded that the analyses incorporating estimated vial sharing did not produce plausible results and therefore would not form the basis for its decision on the use of azacitidine in the NHS.

4.8 The Committee noted the ERG’s concerns about the manufacturer’s model, mainly relating to the selection of the parametric function to model overall survival. The ERG stated that the most important influence on the model’s outputs was overall survival, and that the choice of parametric distribution used to extrapolate estimates of overall survival from the AZA-001 trial greatly influenced the results. The Committee noted that the manufacturer’s final base case used the lognormal distribution to extrapolate overall survival from the trial data, which the manufacturer justified with supporting data from a Düsseldorf myelodysplastic syndromes registry. The Committee understood that the use of the lognormal distribution modelled survival in such a way that a percentage of patients live to an unrealistic age, given the nature of the condition (see section 3.12). It noted that the Weibull distribution generally provided the best overall fit to the Düsseldorf registry long-term survival data. The Committee therefore concluded that the most plausible ICER was derived from the manufacturer’s sensitivity analysis, which used the Weibull distribution, and which resulted in an ICER of approximately £63,000 per QALY gained for the comparison with best supportive care (including the patient access scheme, see section 3.10).

4.9 The Committee considered the ERG’s concerns that the manufacturer’s estimate of quality of life included in the model
lacked face validity. The patient experts and clinical specialists stated that treatment with azacitidine reduces symptoms (such as fatigue) and the need for blood transfusions, both of which are probably associated with a degree of disutility. The Committee noted, however, that the manufacturer’s model produced small gains in health-related quality of life as a result of treatment with azacitidine, and that greater independence from blood transfusions was not included in the utility estimate. It noted that the manufacturer estimated utility by mapping to the EQ-5D. The EQ-5D does not include fatigue as a dimension, although it would capture some of the effects of fatigue on the patient’s ability to undertake normal activities. The Committee therefore considered that reduced fatigue after azacitidine treatment may not have been completely captured in the modelled utility values. The Committee was aware of the ERG’s concerns about the mapping of EORTC values to the EQ-5D, which is associated with greater uncertainty than calculating utility values directly. Additionally, the Committee considered that because the algorithm had been developed using data from patients with oesophageal cancer, the values would be associated with greater uncertainty than if a validated algorithm based on patients with myelodysplastic syndromes had been used. The Committee also noted that sensitivity analyses carried out by the manufacturer showed that variations in the utility values had relatively little impact on the ICERs. The Committee concluded that the manufacturer’s model may have underestimated the gains in health-related quality of life resulting from treatment with azacitidine, but it was not known by how much. It also concluded that because the ICER estimate was largely driven by the incremental life years gained and was only minimally affected by
the changes in health-related quality of life, the impact of underestimating the gains was likely to be small.

4.10 The Committee noted the ERG’s concerns about the modelling of time to transformation to acute myeloid leukaemia. The Committee noted that the modelled time to transformation was shorter than observed in the AZA-001 trial. The Committee considered that this could impact on total treatment costs as it would affect the proportion of patients remaining on treatment and how much treatment was received. The Committee further considered the use of costs in the model. It considered that the use of the NHS 2009/10 tariff was appropriate because it could provide a more precise estimate of hospital costs by breaking down costs attributable to adverse events. The Committee concluded that the modelled increased costs of weekend administration were reasonable; noting that the associated impact on the ICERs was relatively low.

4.11 The Committee considered supplementary advice from NICE that should be taken into account when appraising treatments that may extend the life of patients with a short life expectancy and that are licensed for indications that affect small numbers of people with incurable illnesses. For this advice to be applied, all the following criteria must be met.

- The treatment is indicated for patients with a short life expectancy, normally less than 24 months.
- There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment.
• The treatment is licensed or otherwise indicated for small patient populations.

In addition, when taking these criteria into account, the Committee must be persuaded that the estimates of the extension to life are robust and that the assumptions used in the reference case economic modelling are plausible, objective and robust.

4.12 The Committee discussed whether the benefit provided by azacitidine for the treatment of myelodysplastic syndromes, chronic myelomonocytic leukaemia and acute myeloid leukaemia fulfilled the criteria for consideration as a life-extending, end-of-life treatment. The Committee understood that there were approximately 700 patients with IPSS intermediate-2 and high-risk myelodysplastic syndromes in England and Wales. The Committee considered that life expectancy with best supportive care alone was likely to be approximately 11.5 months. It considered the evidence from the AZA-001 trial and noted that the median overall survival for patients treated with azacitidine in the best supportive care stratification group was 21.1 months. The Committee agreed that azacitidine would improve the treatment of myelodysplastic syndromes, chronic myelomonocytic leukaemia and acute myeloid leukaemia and that it was likely that azacitidine would increase overall survival by approximately 9.6 months. The Committee took the view that the estimates of clinical effectiveness informing the best available estimate of the ICER were sufficiently robust to conclude that azacitidine meets the criteria for being a life-extending, end-of-life treatment.

4.13 The Committee then considered the ICER taking into account the end-of-life considerations. It considered the best available estimate
of the base-case ICER to be approximately £63,000 per QALY gained (see section 4.8). It considered that the additional weight that would need to be assigned to the original QALY benefits in this patient group for the cost effectiveness of the drug to fall within the current threshold range would be too great. Therefore the Committee concluded that azacitidine would not be a cost-effective use of NHS resources as a treatment for patients with myelodysplastic syndromes, chronic myelomonocytic leukaemia or acute myeloid leukaemia (as listed in section 2.1).

4.14 The Committee considered whether there were any subgroups of patients for whom azacitidine would be considered a cost-effective use of NHS resources, and whether NICE’s duties under the equalities legislation required it to alter or to add to its recommendations in any way. The Committee acknowledged that the manufacturer had presented data for the pre-randomisation stratification groups (that is, for people who were eligible to receive treatment with chemotherapy). The Committee noted that it had been presented with evidence indicating that there are no clear or consistent criteria by which these patients would be identified (see section 4.2). It therefore considered that it would be inappropriate to make any recommendations for the pre-randomisation stratification groups (that is, for specific groups defined by their eligibility for chemotherapy). The Committee noted that azacitidine may be of specific benefit to those who are unable to receive blood transfusions for clinical or religious reasons. The Committee noted that patients treated with azacitidine required fewer blood transfusions than patients treated with best supportive care. However, the Committee noted that no representations had been made or evidence received about the pathway of care for patients with myelodysplastic syndromes, chronic myelomonocytic
leukaemia or acute myeloid leukaemia who are unable to receive blood transfusions, or about the effectiveness of azacitidine in this patient population. The Committee considered that because the most plausible ICER for azacitidine in the general patient population was approximately £63,000 per QALY gained, it would be inappropriate to make recommendations for a subgroup defined by its inability to receive blood transfusions without any evidence on how the characteristics of those subgroups affect the estimates of azacitidine’s cost effectiveness. The Committee therefore concluded that it could not recommend the use of azacitidine in any subgroups of patients with myelodysplastic syndromes, chronic myelomonocytic leukaemia or acute myeloid leukaemia (as listed in section 2.1).

5 Implementation

5.1 The Secretary of State and the Welsh Assembly Minister for Health and Social Services have issued directions to the NHS on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends use of a drug or treatment, or other technology, the NHS must provide funding and resources for it within 3 months of the guidance being published. If the Department of Health issues a variation to the 3-month funding direction, details will be available on the NICE website. The NHS is not required to fund treatments that are not recommended by NICE.

5.2 NICE has developed tools to help organisations put this guidance into practice (listed below). These are available on our website (www.nice.org.uk/TAXXX).

- Slides highlighting key messages for local discussion.
• Costing report and costing template to estimate the savings and costs associated with implementation.
• Implementation advice on how to put the guidance into practice and national initiatives that support this locally.
• A costing statement explaining the resource impact of this guidance.
• Audit support for monitoring local practice.

6 Recommendations for further research

6.1 The Committee recommends that a study estimating utilities using directly observed health-related quality of life values (such as EQ-5D scores) in patients with myelodysplastic syndromes, chronic myelomonocytic leukaemia or acute myeloid leukaemia is conducted.

7 Related NICE guidance

Published
• Improving outcomes in haematological cancers. NICE cancer service guidance (2003). Available from guidance.nice.org.uk/CSGHO

8 Review of guidance

8.1 The guidance on this technology will be considered for review in February 2013. NICE welcomes comment on this proposed date. The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.
Ken Stein
Vice Chair, Appraisal Committee
February 2010
Appendix A: Appraisal Committee members and NICE project team

A Appraisal Committee members

The Appraisal Committees are standing advisory committees of NICE. Members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. There are four Appraisal Committees, each with a chair and vice chair. Each Appraisal Committee meets once a month, except in December when there are no meetings. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Professor Keith Abrams
Professor of Medical Statistics, University of Leicester

Dr Amanda Adler (Chair from September 2009)
Consultant Physician, Addenbrooke's Hospital, Cambridge

Dr Ray Armstrong
Consultant Rheumatologist, Southampton General Hospital

Dr Jeff Aronson
Reader in Clinical Pharmacology, University Department of Primary Health Care, University of Oxford
Dr Darren Ashcroft
Reader in Medicines Usage and Safety, School of Pharmacy and Pharmaceutical Sciences, University of Manchester

Professor David Barnett (Chair until September 2009)
Professor of Clinical Pharmacology, University of Leicester

Dr Peter Barry
Consultant in Paediatric Intensive Care, Leicester Royal Infirmary

Dr Michael Boscoe
Consultant Cardiothoracic Anaesthetist, Royal Brompton and Harefield NHS Foundation Trust

Professor John Cairns
Professor of Public Health and Policy, London School of Hygiene and Tropical Medicine

Dr Mark Chakravarty
External Relations Director, Pharmaceuticals and Personal Health, Oral Care Europe

Dr Martin Duerden
Medical Director, Conwy Local Health Board

Dr Fergus Gleeson
Consultant Radiologist, Churchill Hospital, Oxford

Ms Sally Gooch
Independent Nursing and Healthcare Consultant

Mrs Eleanor Grey
Lay member
Mr Sanjay Gupta
Former Service Manager in Stroke, Gastroenterology, Diabetes and Endocrinology, Basildon and Thurrock University Hospitals Foundation NHS Trust

Dr Neil Iosson
General Practitioner

Mr Terence Lewis
Lay member

Professor Gary McVeigh
Professor of Cardiovascular Medicine, Queen's University, Belfast

Dr Ruairidh Milne
Director of Strategy and Development and Director for Public Health Research at the NIHR Evaluation, Trials and Studies Coordinating Centre at the University of Southampton

Dr Rubin Minhas
General Practitioner and Clinical Director, BMJ Evidence Centre

Mr Stephen Palmer
Senior Research Fellow, Centre for Health Economics, University of York

Dr Sanjeev Patel
Consultant Physician and Senior Lecturer in Rheumatology, St Helier University Hospital

Dr John Pounsford
Consultant Physician, Frenchay Hospital, Bristol
Mr Philip Pugh
Strategic Development Lead for Healthcare Associated Infection and Antimicrobial Resistance, Health Protection Agency

Dr Florian Alexander Ruths
Consultant Psychiatrist and Cognitive Therapist at the Maudsley Hospital, London

Mr Navin Sewak
Primary Care Pharmacist, NHS Hammersmith and Fulham

Dr Stephen Saltissi
Consultant Cardiologist, Royal Liverpool University Hospital

Dr Lindsay Smith
General Practitioner, East Somerset Research Consortium

Mr Roderick Smith
Finance Director, West Kent Primary Care Trust

Mr Cliff Snelling
Lay member

Professor Ken Stein (Vice Chair)
Professor of Public Health, Peninsula Technology Assessment Group (PenTAG), University of Exeter

Professor Andrew Stevens
Professor of Public Health, Department of Public Health and Epidemiology, University of Birmingham

Dr Rod Taylor
Associate Professor in Health Services Research, Peninsula Medical School, Universities of Exeter and Plymouth
Ms Nathalie Verin  
Health Economics Manager, Boston Scientific UK and Ireland

Dr Colin Watts  
Consultant Neurosurgeon, Addenbrooke’s Hospital, Cambridge

Mr Tom Wilson  
Director of Contracts and Information Management and Technology, Milton Keynes Primary Care Trust

B NICE project team

Each technology appraisal is assigned to a team consisting of one or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Whitney Miller  
Technical Lead

Prashanth Kandaswamy  
Technical Adviser

Dr Bhash Naidoo  
Technical Adviser

Jeremy Powell  
Project Manager
Appendix B: Sources of evidence considered by the Committee

A  The Evidence Review Group (ERG) report for this appraisal was prepared by the West Midlands Health Technology Assessment Collaboration:


The Decision Support Unit (DSU) prepared a report for this appraisal:

- Miners A. DSU report for NICE – Azacitidine STA economic model 09/12/09, December 2009

B  The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope, the ERG report and the appraisal consultation document (ACD). Organisations listed in I were also invited to make written submissions. Organisations listed in II and III had the opportunity to give their expert views. Organisations listed in I, II and III also have the opportunity to appeal against the final appraisal determination.

I  Manufacturer/sponsor:

- Celgene

II  Professional/specialist and patient/carer groups:

- British Committee for Standardisation in Haematology
- British Society for Haematology
- Cancer Research UK
- Leukaemia CARE
III Other consultees:

- Department of Health
- Harrow PCT
- Stockton-On-Tees PCT
- Welsh Assembly Government

IV Commentator organisations (did not provide written evidence and without the right of appeal):

- Department of Health, Social Services and Public Safety for Northern Ireland
- National Collaborating Centre for Cancer
- NHS Quality Improvement Scotland
- Pharmacia
- West Midlands Health Technology Assessment Collaboration
- Winthrop Pharmaceuticals UK

C The following individuals were selected from clinical specialist and patient advocate nominations from the non-manufacturer/sponsor consultees and commentators. They gave their expert personal view on azacitidine by attending the initial Committee discussion and providing written evidence to the Committee. They were also invited to comment on the ACD.

- Dr David T Bowen, Consultant Haematologist, nominated by the NCRI Haematological Oncology Clinical Studies Group/RCP/RCR/ACP/JCCO – clinical specialist
• Dr Dominic J Culligan, Consultant Haematologist, nominated by the Royal College of Pathologists and British Committee for Standardisation in Haematology – clinical specialist
• Mr Paul Harford, nominated by MDS UK – patient expert
• Ms Stella Pendleton, nominated by the Rarer Cancers Forum – patient expert

Representatives from the following manufacturer/sponsor attended Committee Meetings. They contributed only when asked by the Committee chair to clarify specific issues and comment on factual accuracy.

• Celgene