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 recommended as a treatment option for adults who are not eligible for haematopoietic stem cell transplantation and have:

- intermediate-2 and high-risk myelodysplastic syndromes according to the International Prognostic Scoring System (IPSS) **or**
- 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

and

- if the manufacturer provides azacitidine with the discount agreed as part of the patient access scheme.

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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 who 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/m^2 of body surface area. The SPC states that patients

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should be pre-medicated with anti-emetics to prevent nausea and vomiting. The list price of azacitidine is £321 for a 100-mg vial (excluding VAT; 'British national formulary' [BNF] edition 60). Based on a body surface area of 1.7 m^2 and a dose of 75 mg/m^2, fourteen vials would be required for one cycle (two vials for each day of treatment). Costs may vary in different settings because of negotiated procurement discounts.

2.4 The manufacturer had 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 would be available with a discount applied to all invoices (referred to as the 'original' patient access scheme in this document). The manufacturer subsequently proposed a revised patient access scheme, in which the discount level is revised and is commercial-in-confidence (see section 5.3). The Department of Health has agreed that the revised patient access scheme can be included in this appraisal in January 2011. The manufacturer has agreed that the revised patient access scheme will remain in place until the publication of reviewed NICE guidance.

3 The manufacturer's submission

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

3.1 The main evidence for the efficacy of azacitidine in patients with high- and intermediate-2 risk myelodysplastic syndromes, chronic myelomonocytic leukaemia or acute myeloid leukaemia in the

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manufacturer's submission was obtained from a phase III, open-label, multicentre, randomised controlled trial (AZA-001; n = 358). Supplementary data from an open-label extension trial of AZA-001 were also provided. Before randomisation, patients were preselected by the investigator (on the basis of age, general condition, comorbidities and patient preference) 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 were then randomised to receive either azacitidine or the preselected conventional care regimen. 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. However, within the conventional care regimens, patients preselected to receive low- or standard-dose chemotherapy tended to be younger and have a higher ECOG performance status than patients preselected to receive best supportive care alone. 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 (59%) were preselected for best supportive care alone, 49 (27%) for low-dose chemotherapy and 25 (14%) for standard-dose chemotherapy. Of the 179 patients receiving azacitidine, 117 (65%) had been preselected for best supportive care alone, 45 (25%) for low-dose

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chemotherapy and 17 (9%; percentages do not add up to 100% because of rounding) 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 stated 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 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 also reported results within each of the preselection groups. Treatment with azacitidine led to statistically significant improvements in overall survival in the group preselected for best supportive care alone and in the group preselected for low-dose chemotherapy plus best supportive care, but not in the group preselected for standard-dose chemotherapy plus best-supportive care. Only patients preselected for best supportive care alone had statistically significant improvement with azacitidine 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 no longer needed transfusions

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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 patients receiving conventional care regimens.

3.4   The ERG considered the results from AZA-001 to be robust and to show 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. The ERG considered that this means that the effectiveness of azacitidine in clinical practice could be lower than that seen in AZA-001. In addition, the ERG noted that the results for the comparison with low- and standard-dose 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 AZA-001 (see section 3.1). Patients entered the model in the myelodysplastic syndromes health state at the start of treatment and left the model at death. The model used a 35-day cycle with a lifetime horizon.

3.6   The manufacturer's economic model used data from AZA-001 and its open-label extension trial to estimate effectiveness. The economic model underwent a number of iterations after clarification requests from the Committee, the ERG and the DSU. The

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manufacturer's base-case analysis used a lognormal parametric function to extrapolate the overall survival from the data 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 AZA-001.

3.7   The manufacturer reported that no quality of life data were collected in AZA-001 that could be used to populate the economic model. Utility value estimates for patients treated with azacitidine and best supportive care 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 a study in patients with oesophageal cancer. Utility value estimates for patients treated with chemotherapy were mapped to the EQ-5D from SF-12 scores published in a report about 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.

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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, which involves treating multiple patients on the same day, could be used for 49% of patients. The reduction in unused vials and consequent savings in drug costs resulting from vial sharing were explored in a scenario analysis.

3.9   The manufacturer's base-case results (using the lognormal parametric function to extrapolate overall survival and excluding any patient access scheme; see section 3.6) gave incremental cost-effectiveness ratios (ICERs) for treatment with azacitidine compared with each of the conventional care regimens of £47,432 per quality-adjusted life year (QALY) gained for patients in the best supportive care alone group, £40,754 per QALY gained for patients in the low-dose chemotherapy group, and £37,105 per QALY gained 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 alone, low-dose chemotherapy and standard-dose chemotherapy groups respectively. Incorporating the original 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

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supportive care alone, 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 original patient access scheme. For the analyses using the Weibull survival function, the ICERs were £63,177 per QALY gained for the best supportive care alone 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 alone 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 lognormal survival function, the ICERs were £45,538 per QALY gained for the best supportive care alone 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 alone 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 analyses of the preselected conventional care groups in AZA-001. 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.

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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 AZA-001, its open-label extension trial 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.

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 values. The ERG reported that the algorithm used to derive the utility values 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

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were potentially very different. The ERG stated that the utility values resulting from the algorithm should be treated with caution.

3.15   The manufacturer explored the impact of adjusting the utility values to account for the differences in the baseline patient characteristics. This was shown to have little impact on the ICERs.

3.16   After the appeal, the manufacturer submitted information on the proportions of patients with high-risk myelodysplastic syndromes, chronic myelomonocytic leukaemia or acute myeloid leukaemia receiving low-dose chemotherapy plus best supportive care and the proportions of patients receiving best supportive care alone. This information included:

- a survey of 72 UK haematologists, with the proportions of patients treated with each conventional care regimen between 2008 and 2010 who were eligible for azacitidine according to the marketing authorisation

- a survey of 23 UK hospitals, with the proportions of patients treated with each conventional care regimen and

- data from the Haematological Malignancy Research Network registry (HMRN; collecting data from 22 hospitals in the Yorkshire and Humber and Yorkshire Coast cancer networks) on the first-line treatment of patients with myelodysplastic syndromes, chronic myelomonocytic leukaemia or acute myeloid leukaemia between September 2004 and August 2009.

The hospital survey and HMRN registry data included all patients with high-risk myelodysplastic syndromes, chronic myelomonocytic leukaemia or acute myeloid leukaemia, not just patients who would be eligible for azacitidine according to the marketing authorisation. The haematologist survey data and hospital survey data were

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presented graphically and indicated that the majority of patients received best supportive care alone, although this proportion appeared lower among the haematologists identified as specialist consultants and among the hospitals identified as specialist centres. The audit of the HMRN registry data showed that of those patients considered as IPSS intermediate-2 or IPSS high risk, 58% received best supportive care alone (including observation only), 12% received low-dose chemotherapy and 28% received standard-dose chemotherapy (2% of patients died before treatment).

3.17   The DSU provided a critique of the three sources of information. The survey of 72 UK haematologists was based on clinicians' estimates of patients receiving each conventional care regimen, rather than the proportions of patients who were eligible for each regimen. Because it was not clear whether the data provided were from case note review or from clinician self-reporting, the DSU considered that the survey was subject to a high risk of bias. For this reason the DSU considered that this survey did not provide reliable data to inform the Committee's considerations about the conventional care regimens. Regarding the survey from 23 UK hospitals, the DSU commented that because the data had been presented graphically it was difficult to estimate the exact proportions of patients treated with each care regimen. The survey was considered to offer limited information because:

- patients who would not be eligible to receive azacitidine were included and
- there was a lack of information about whether the sample of hospitals was representative of all UK hospitals and about the methods of data collection.

In the DSU's view, the HMRN registry provided the most objective and reliable data for the numbers of patients receiving conventional care regimens. In summary, the DSU expressed the view that the three sources of information provided only a limited evidence base for the use of low-dose chemotherapy and confirmed the current variation in clinical practice.

3.18   After the appeal, the manufacturer also submitted information about the clinical characteristics of patients receiving each of the conventional care regimens in routine clinical practice. This included the results of an 'informal literature review' by the manufacturer and the clinical characteristics of patients receiving low-dose chemotherapy from the survey of UK haematologists. The manufacturer reported that among patients who were eligible for azacitidine according to the marketing authorisation, low-dose chemotherapy was most widely used in the UK in patients with the following characteristics:

- symptomatic cytopenias:
    - anaemia requiring transfusion
    - neutropenia 0.5–1.0×10^9/litre (with or without infectious episodes)
    - thrombocytopenia 30–100×10^9/litre
- normal karyotype (or one cytogenetic abnormality)
- limited comorbidities, with Haematopoietic Cell Transplantation-specific Comorbidity Index (HCTCI) score 0–2
- ECOG performance status 0–2
- logistically able to undergo treatment.

3.19   The DSU commented that only two of the eleven studies provided by the manufacturer after the appeal were conducted in the UK and

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only one had been published since 1991. It was not clear how the characteristics had been selected from these studies; in particular toxicity and administration had been identified in the literature review but did not appear in the final list of characteristics. However, the HCTCI score, which the manufacturer previously reported was not in routine clinical use in the UK, was included in the list. In summary, the DSU considered that the literature review offered limited evidence on eligibility criteria for patients receiving the conventional care regimens.

3.20   After the appeal, the manufacturer also submitted additional cost-effectiveness analyses incorporating health-related quality of life data from the patient group MDS UK. The manufacturer provided analyses:

- separately comparing azacitidine with each conventional care regimen specified by the Appeal Panel (that is, compared with best supportive care alone and compared with low-dose chemotherapy plus best supportive care) and
- comparing azacitidine with usual care (that is, a single estimate representing a weighted average of all the conventional care regimens together).

Each analysis used a Weibull parametric function to extrapolate overall survival, assumed no vial sharing, and included the original patient access scheme.

3.21   The manufacturer's analyses submitted after the appeal indicated that azacitidine compared with best supportive care alone was associated with an incremental cost of £63,756 and an incremental QALY gain of 1.01, producing an ICER of £63,177 per QALY gained. Azacitidine compared with low-dose chemotherapy was

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associated with an incremental cost of £65,671 and an incremental QALY gain of 1.34, giving an ICER of £49,030 per QALY gained. Azacitidine compared with usual care (a weighted average of all the conventional care regimens together) was associated with an incremental cost of £61,801 and an incremental QALY gain of 1.09, giving an ICER of £56,945 per QALY gained. The manufacturer's submission stated that this weighted average was calculated using the proportion of patients receiving each of the conventional care regimens in AZA-001 (that is, 62% for best supportive care alone, 26% for low-dose chemotherapy plus best supportive care and 12% for standard-dose chemotherapy plus best supportive care).

3.22 The DSU commented that the utility values used in the revised economic evaluation were based on descriptions of health states that included dependence or independence from transfusion as a feature and did not separate the specific utility value of dependence or independence from transfusion from that of associated symptoms. It noted the small numbers of patients in the study (n = 47) and patients from the UK (n = 21). The DSU further noted that the data did not capture adverse events, in contrast with the utility value estimates used in the manufacturer's original base case. The DSU commented that constant utility values had been applied over the time horizon of the model, assuming that a patient's dependence on transfusion would remain constant throughout their treatment period. It considered that this was an unreasonable assumption. The DSU concluded that the MDS utility data did not provide more appropriate information for the economic evaluation than the data used in the manufacturer's base case. However, the DSU ran exploratory analyses using data from all patients in the MDS UK study and then with only data from the UK patients. None of these exploratory analyses resulted in significant

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changes to the cost-effectiveness estimates provided by the manufacturer.

3.23   The DSU considered that the analysis using a weighted average (see section 3.21) was not an appropriate measure of the cost effectiveness of azacitidine. The DSU took the view that the appropriate approach would be to consider all the treatment options in a single incremental analysis, comparing each treatment with the next most effective alternative, and excluding any dominated (that is, more costly and less effective) treatments from the analysis.

3.24   In response to the appraisal consultation document produced after the appeal, the manufacturer submitted updated cost-effectiveness analyses. Each analysis was deterministic, used a Weibull parametric function to extrapolate overall survival, assumed no vial sharing, and included the revised patient access scheme (see section 2.4). These analyses estimated the following ICERs for azacitidine, compared with three alternative weighted averages of the conventional care regimens:

- £49,405 per QALY gained, based on the proportions of patients that had received one of the conventional care regimens after randomisation in AZA-001 (of which 59% patients received best supportive care alone, 27% received low-dose chemotherapy and 14% received standard-dose chemotherapy)

- £49,837 per QALY gained, based on the proportions of IPSS intermediate-2 or high-risk patients that had received one of the conventional care regimens in the HMRN registry (of which 59% patients received best supportive care alone,

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12% received low-dose chemotherapy and 28% received standard-dose chemotherapy)

- £50,920 per QALY gained, based on the proportions of patients with the 'refractory anaemia with excess blasts' (RAEB) disease subtype that had received one of the conventional care regimens in the HMRN registry (of which 69% patients received best supportive care alone, 13% received low-dose chemotherapy and 18% received standard-dose chemotherapy).

3.25   The DSU considered that the most generalisable estimates for conventional care patterns from AZA-001 should be taken from the pre-randomisation proportions (that is, the whole trial population), instead of the proportions of patients (50% of the trial population) randomised to one of the conventional care regimens (as presented by the manufacturer). Before randomisation, 62% of patients were preselected to receive best supportive care alone, 26% received low-dose chemotherapy and 12% received standard-dose chemotherapy. The weighted average ICER associated with these proportions was £49,808 per QALY gained.

3.26   The DSU further considered that probabilistic analyses (instead of the deterministic analyses presented by the manufacturer) would be more robust, and therefore more appropriate for the Committee's consideration. The probabilistic ICERs associated with each of the weighted averages were:

- £47,336 per QALY gained, based on the proportions of patients that had received one of the conventional care regimens after randomisation in AZA-001

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- £47,782 per QALY gained, based on the proportions of patients preselected (that is, prior to randomisation) to receive one of the conventional care regimens in AZA-001

- £47,224 per QALY gained, based on the proportions of IPSS intermediate-2 or high-risk patients allocated to conventional care regimens in the HMRN registry

- £48,581 per QALY gained, based on the proportions of patients with the RAEB disease subtype allocated to conventional care regimens in the HMRN registry.

3.27   Full details of all the evidence are in the manufacturer's submissions, the ERG report and the DSU reports, which are available from www.nice.org.uk/TAXXX

4   Consideration of the evidence

4.1   The Appraisal Committee (appendix A) 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.

4.2   The Committee heard from the clinical specialists that current practice includes the use of best supportive care and, for some patients who are able to tolerate it, low- or standard-dose chemotherapy. However, the Committee heard from the clinical specialists that there was no nationally recognised standard of care for patients with myelodysplastic syndromes, chronic myelomonocytic leukaemia or acute myeloid leukaemia, particularly

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regarding patients' eligibility for chemotherapy. The Committee noted survey and HMRN registry data provided by the manufacturer, which together showed variations in treatment patterns among UK haematologists. The survey data showed a wide variation in clinicians' views about what determines a patient's eligibility for chemotherapy. The Committee heard from the clinical specialists that the group of patients eligible for chemotherapy could only be broadly described because of the current lack of consensus among UK haematologists about whether chemotherapy is appropriate for patients with certain comorbidities or disease-specific characteristics, and because of the inability to quantify clinician and patient preference for treatment. The Committee concluded that while best supportive care, low-dose and standard-dose chemotherapy were currently being used to treat patients with myelodysplastic syndromes, chronic myelomonocytic leukaemia or acute myeloid leukaemia, there was no consensus among clinicians on the set of clinical characteristics that could identify patients for whom chemotherapy should be a treatment option.

4.3 The Committee considered the quality of life of patients with myelodysplastic syndromes, chronic myelomonocytic leukaemia and acute myeloid leukaemia. The Committee understood from the evidence submitted, and from the evidence of clinical specialists and patient experts, that fatigue and a reduced ability to carry out day-to-day activities are common in these conditions and have a negative impact on patients' quality of life. The Committee noted information from patient groups, who reported that dependence on blood transfusions is an important aspect of these conditions and also has a negative impact on quality of life. The Committee concluded that having myelodysplastic syndromes decreases

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quality of life, and aspects of current conventional care (such as the need for blood transfusions) have a further negative impact on quality of life.

Clinical effectiveness

4.4   The Committee considered the clinical-effectiveness evidence from AZA-001 presented by the manufacturer. 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, the presence of comorbidities and patient preference. It also understood that patients randomised to treatment with azacitidine were compared with patients in their respective pre-randomisation regimen. The Committee also heard from the clinical specialists that the proportion of patients in each preselection group in AZA-001 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).

4.5   The Committee noted that the median overall survival for patients receiving azacitidine was longer than for patients receiving the conventional care regimens. The Committee further noted that median time to transformation to acute myeloid leukaemia was longer for patients receiving azacitidine and the percentage of patients becoming independent of blood transfusions was higher for patients receiving azacitidine than for patients receiving the conventional care regimens. The Committee noted that when outcomes were analysed separately for each conventional care regimen, the difference in overall survival between the treatment arms in the standard-dose chemotherapy group was not statistically

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significant, and the differences between the treatment arms in the estimates of time to transformation to acute myeloid leukaemia for either the low-dose or standard-dose chemotherapy groups were not statistically significant. The Committee was aware that the small patient numbers limited the precision and certainty of the outcome estimates in these groups, but concluded that the estimates of total overall survival compared with conventional care 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.

4.6 The Committee considered the role of patient preference in the design and analysis of AZA-001. The Committee heard from the DSU and the manufacturer that the term 'patient preference trial' is used to describe trial designs that take account of a patient's preference to receive either the study treatment (for example, azacitidine) or the comparator (for example, conventional care). It noted that in AZA-001, patient preference informed preselection to one of the conventional care regimens before randomisation, but did not inform randomisation to either azacitidine or conventional care. The Committee concluded that the role of patient preference in AZA-001 did not affect the way in which the trial results or subsequent analyses should be considered.

4.7 The Committee considered the potential adverse effects associated with treatments for myelodysplastic syndromes and the impact of these effects on quality of life. The Committee heard from the clinical specialists that common adverse effects of treatment with azacitidine include peripheral blood cytopenias, myelosuppression, nausea, vomiting and injection site reactions. The patient experts

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and clinical specialists agreed that these adverse effects are generally well tolerated. The Committee heard from the patient experts that compared with other treatment options, azacitidine was associated with relief from fatigue, fewer infection-related hospitalisations, a decreased need for blood and platelet transfusion, and increased ability to perform day-to-day activities. The Committee noted that no quality of life data were collected in AZA-001, although EORTC data collected in CALGB 9221 suggested improvements in overall health with azacitidine.

4.8   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

4.9   The Committee considered evidence on the cost effectiveness of azacitidine for the treatment of myelodysplastic syndromes, chronic myelomonocytic leukaemia and acute myeloid leukaemia. It discussed the likelihood of vial sharing, noting that because of the small number of patients, it may be difficult to implement a vial-sharing scheme. It concluded that the manufacturer's estimate of 49% of patients being able to receive treatment at the same time (and therefore share vials) 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.

4.10   The Committee noted the ERG's concerns about the manufacturer's initial model, mainly relating to the selection of the

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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 AZA-001 greatly influenced the results. The Committee noted that the manufacturer's initial base case used the lognormal function 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 some patients were predicted to live to an unrealistic age given the nature of the condition (see section 3.12), that is the use of lognormal distribution led to an overestimation of survival. The Committee concluded that the Weibull distribution generally provided the best overall fit to the Düsseldorf registry long-term survival data, and that modelling that incorporated the Weibull distribution should be used to inform a decision on the use of azacitidine in the NHS.

4.11   The Committee considered the estimates of quality of life included in the model (see also sections 4.12 and 4.13). The Committee first considered the derivation of the utility values. It was aware of the ERG's concerns about the mapping of EORTC values to the EQ-5D (see section 3.14). The Committee concluded 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, chronic myelomonocytic leukaemia and acute myeloid leukaemia had been used.

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4.12   The Committee then considered the face validity of the quality of life gains attributed to azacitidine in the model. The patient experts and clinical specialists stated that treatment with azacitidine reduces symptoms (such as fatigue) and the need for blood transfusions. The Committee agreed that the associated utility gains of these should ideally be reflected in the model. The Committee noted that greater independence from blood transfusions was not explicitly included in the utility value estimate. It was aware that the manufacturer estimated the utility value by mapping to the EQ-5D. The Committee understood that 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 day-to-day activities. The Committee also understood that the EORTC measure includes a domain that captures the impact of treatment on quality of life, and that dependence on transfusion could be expected to affect this. It considered that reduced fatigue after azacitidine treatment may not have been completely captured in the modelled utility values. The Committee noted the alternative utility values provided by MDS UK after the appeal, which were meant to better reflect the utility values associated with dependence on or independence from blood transfusions. However, the Committee noted the DSU's concern that the alternative utility values did not separate dependence or independence from transfusion from associated symptoms (see section 3.22) and it did not accept these in preference to the manufacturer's previous estimates. The Committee also noted that the model applied constant utility values within each health state, therefore assuming quality of life gains from the first day of treatment, which it considered unrealistic. Taking all these points into account, the Committee concluded that it was uncertain

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whether the utility values used in the model under- or over-estimated the true utility values associated with myelodysplastic syndromes.

4.13 The Committee considered the uncertainty around the quality of life estimates included in the model (see sections 4.11 and 4.12). The Committee noted that sensitivity analyses carried out by the manufacturer showed that variations in the utility values had relatively little impact on the ICERs. It concluded that because the ICER estimate was largely driven by the incremental life years gained and the acquisition cost of azacitidine, and was only minimally affected by the changes in health-related quality of life, the impact of any over- or underestimation of quality of life gains was likely to be small.

4.14 The Committee considered the inclusion of costs in the economic model. The Committee noted the use of the NHS 2009/2010 tariff. It considered that using 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 also noted the assumed increase in the cost for treatment received at the weekend. The Committee concluded that the modelled increased costs of weekend administration were reasonable, aware that the associated impact on the ICERs was relatively small. On balance, the Committee concluded that costs included in the model were acceptable.

4.15 The Committee considered the estimated cost effectiveness of azacitidine. The Committee noted that the manufacturer had submitted two approaches to estimating the ICERs for azacitidine:

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- one analysis comparing azacitidine separately with each of the conventional care regimens specified by the Appeal Panel (that is, compared with best supportive care alone and compared with low-dose chemotherapy plus best supportive care) and

- three analyses comparing azacitidine with usual care (that is, a single estimate representing a weighted average of all the conventional care regimens together), with each analysis using different proportions of conventional care to form the weighted average.

The Committee noted that no cost-effectiveness evidence was presented for the subgroup of patients with the −7/del(7q) chromosomal abnormality.

4.16   The Committee considered the two approaches to estimating the cost effectiveness of azacitidine. The Committee first considered the separate conventional care regimen analyses. The Committee noted that patients randomised to receive azacitidine in the group preselected to receive low-dose chemotherapy plus best supportive care incurred higher total costs (£101,100) than those randomised to azacitidine who had been preselected to receive best supportive care alone (£91,800). It further noted that the number of total QALYs (that is, not the incremental QALY gain) was greater in those randomised to azacitidine who had been preselected to receive low-dose chemotherapy (2.44) than in those randomised to azacitidine who had been preselected to receive best supportive care alone (2.04). The Committee also noted that in the analyses presented before the appeal comparing azacitidine with standard-dose chemotherapy, the number of QALYs associated with those randomised to azacitidine who had been preselected to receive standard-dose chemotherapy in the azacitidine arm was 1.91. The

Committee concluded that there appeared to be no reason, other than differences in baseline patient characteristics, why those who were randomised to azacitidine but were preselected to receive low-dose chemotherapy should have gained greater benefit than those who were randomised to azacitidine but were preselected to receive standard-dose chemotherapy plus best supportive care or best supportive care alone. The Committee agreed that this uncertainty should be noted when considering the most appropriate analyses on which to base its recommendations.

4.17   The Committee then considered the analyses of azacitidine compared with a weighted average of usual care (see sections 3.24 to 3.26). The Committee understood that the weighted ICERs had each been calculated by combining the individual ICERs for the respective conventional care regimens, each weighted by the proportion of patients receiving these regimens in AZA-001 and in the HMRN registry respectively. The Committee understood the significant methodological limitations associated with analyses involving the use of such a weighted average, in particular the need for equivalent patient characteristics (such as age or disease severity) at baseline among any of the groups being combined (see section 4.16). It also acknowledged the importance of ensuring that the full range of appropriate comparators was considered within these groups. It noted that because of differences in the baseline patient characteristics of the conventional care regimen subgroups (see section 3.1) the patient populations and associated population-specific results may not necessarily be appropriate for statistical analysis, which combines estimates across the groups using a simple weighted average.

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4.18   The Committee then considered which of the two analytical approaches to considering cost effectiveness provided the most appropriate basis for its decision. It agreed that the most important consideration in whether a decision should be based on the separate comparisons with the different conventional care regimens was the need for a clear definition of the groups of patients eligible to receive each of the conventional care regimens. The Committee agreed that because a set of clear and objective clinical characteristics defining the eligibility of patients to receive chemotherapy had not been agreed among haematologists, it could not make recommendations based on any of the separate conventional care regimen groups (see section 4.2).

4.19   The Committee was aware of the significant methodological limitations with using weighted averages. The Committee understood that weighted averages can mask differences in the incremental costs and/or QALYs of the technologies being combined. The Committee was aware that the NICE 'Guide to the methods of technology appraisal' states that best practice should be considered as a comparator for appraisal of health technologies. If best practice is defined as a cost-effective treatment option, the standard approach to assessing the cost effectiveness of azacitidine in this context would be to consider all treatment options (that is, each of the conventional care regimens) in an iterative incremental analysis (that is, assessing the ratio of the additional cost and benefit of each technology compared with the next best alternative) to identify the most cost-effective strategy. The Committee understood that the weighted average approach assumes that each conventional care regimen is the most cost-effective treatment option available for the patient group for whom it is used. It heard from the DSU that the necessary evidence to test

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this assumption is not available, given the remit of this appraisal, and therefore the use of a weighted average would result in some uncertainty in the ICER produced. It further heard from the DSU that if the cost effectiveness of each of the individual conventional care regimens was not established, the magnitude and direction of uncertainty in the weighted average ICER is unknown. The Committee also understood that because the populations eligible for each of the conventional care regimens cannot be clearly defined (see section 4.2), an incremental analysis (as preferred by the DSU) is not possible in this case. Taking into account the limitations of the available evidence and in the absence of a satisfactory alternative, the Committee hesitantly concluded that any decision on the cost effectiveness of azacitidine would need to be made using the weighted average.

4.20   The Committee considered the proportions of each conventional care regimen used to calculate the weighted average. It understood that the manufacturer's base-case estimate was based on the proportions of people receiving each conventional care regimen in AZA-001, but that alternative analyses used the HMRN registry data submitted by the manufacturer (see section 3.25). The Committee heard from the clinical specialists that the HMRN registry, a UK database of over 600 patients, provided a representative estimate of the management of myelodysplastic syndromes in the UK. It noted that the HMRN registry includes a wider range of patients than those covered by the marketing authorisation for azacitidine but acknowledged clinical advice that within the HMRN registry, the subset of patients classified as having IPSS intermediate-2 or high-risk myelodysplastic syndromes provided the best available estimate of the proportion of patients receiving each of the conventional care regimens in the patient

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population for whom azacitidine is licensed. The Committee concluded that a weighted average of conventional care regimens should be calculated using the HMRN registry data (for the subset of patients having IPSS intermediate-2 or high-risk myelodysplastic syndromes) rather than the AZA-001 data.

4.21   The Committee considered the ICERs calculated using a weighted average of the proportions receiving conventional care regimens in the HMRN registry for patients classified as IPSS intermediate-2 or high risk. It understood that in this patient population approximately 59% of patients received best supportive care alone, 12% received low-dose chemotherapy plus best supportive care and 29% received standard-dose chemotherapy plus best supportive care. The Committee noted that the manufacturer's deterministic ICER using these proportions of patients was £49,800 per QALY gained. The Committee heard from the DSU that the probabilistic estimate of the ICER associated with these proportions was approximately £47,200 per QALY gained (see section 3.27). The Committee considered that the probabilistic ICER was a more valid estimate than the deterministic estimate because it takes account of joint parameter uncertainty. The Committee noted that because the incremental cost-effectiveness estimates of each respective conventional care regimen that comprise the weighted average were not known (see section 4.19), uncertainty about the true ICER for azacitidine compared with usual care remained. Taking into account the limitations associated with the use of a weighted average and the uncertainty associated with the cost effectiveness of each individual conventional care regimen, the Committee concluded that £47,200 per QALY gained represented the best available estimate of the cost effectiveness of azacitidine.

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4.22   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.

4.23   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 are 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 AZA-001 and noted that the median overall survival for patients treated with azacitidine in the best supportive care

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preselection 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 agreed that the estimates of clinical effectiveness informing the best available estimate of the ICER were sufficiently robust and concluded that azacitidine meets the criteria for being a life-extending, end-of-life treatment.

4.24   The Committee then considered the ICER taking into account the end-of-life considerations. It considered that the best available estimate of the base-case ICER was approximately £47,200 per QALY gained (see section 4.21). The Committee accepted the uncertainty associated with this estimate and acknowledged the difficulty of assessing the impact of uncertainty on the best estimate of the ICER (see section 4.19). The Committee was aware that other technologies had been recommended using the end-of-life criteria with ICERs as high as the one in this appraisal, but was conscious of the increasing cost pressures in the NHS and the opportunity costs that would result from a recommendation to fund a technology with an ICER of this magnitude. However, the Committee recognised that azacitidine represents an important change in the treatment of patients with myelodysplastic syndromes, noting the substantial benefits associated with its use. The Committee considered that on balance, the additional weight that would need to be assigned to the QALY benefits for the cost effectiveness of azacitidine to fall within the current threshold range was acceptable on this occasion. Therefore the Committee considered that azacitidine when provided by the manufacturer with the discount agreed in the revised patient access scheme agreed

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by the Department of Health in January 2011 was a cost-effective use of NHS resources as a treatment option for people with myelodysplastic syndromes, as stated in the marketing authorisation. This includes adults who 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.

4.25   The Committee considered whether NICE's duties under the equalities legislation required it to alter or to add to its recommendations in any way. At an earlier meeting, the Committee noted that azacitidine may be of specific benefit to those who, for clinical or religious reasons, are unable to receive blood transfusions, because patients treated with azacitidine require 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 this particular group of patients, or about the effectiveness of azacitidine in this patient population. Therefore the Committee agreed that it would not be appropriate to make recommendations for a subgroup of patients unable to receive blood transfusions. Because the final recommendations (see section 4.24) do not restrict access to azacitidine for any particular group of patients, the Committee concluded that there was now no need to alter or add to its recommendations in any case.

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Summary of Appraisal Committee's key conclusions

TAXXX	Azacitidine for the treatment of myelodysplastic syndromes, chronic myelomonocytic leukaemia and acute myeloid leukaemia	Section
Key conclusion		
Azacitidine is recommended as a treatment option for adults who are not eligible for haematopoietic stem cell transplantation and have: • intermediate-2 and high-risk myelodysplastic syndromes according to the International Prognostic Scoring System (IPSS) **or** • 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 **and** • if the manufacturer provides azacitidine with the discount agreed as part of the patient access scheme.	1.1
The key drivers for this recommendation were as follows: • Taking into account the end-of-life considerations, the Committee recognised that azacitidine represents an important change in the treatment of patients with myelodysplastic syndromes. • The Committee considered that on balance, with the addition of the revised patient access scheme, azacitidine represented a cost-effective use of NHS resources.	4.24
Current practice		
Clinical need of patients, including the availability of alternative treatments	Best supportive care, low-dose and standard-dose chemotherapy are currently being used to treat patients with myelodysplastic syndromes, chronic myelomonocytic leukaemia or acute myeloid leukaemia who are not eligible for stem cell transplantation. However, there was no consensus among clinicians on the set of clinical characteristics that could identify patients for whom chemotherapy should be a treatment option.	4.2 4.2
	Fatigue and a reduced ability to carry out day-to-day activities are common in these conditions and have a negative impact on patients' quality of life. Dependence on blood transfusions is an important aspect of these conditions and also has a negative impact on	4.3

	quality of life.	
The technology		
Proposed benefits of the technology How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?	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.	4.8
	Compared with other treatment options, azacitidine was associated with relief from fatigue, fewer hospitalisations because of infections, a decreased need for blood and platelet transfusion, and increased ability to perform day-to-day activities.	4.7
What is the position of the treatment in the pathway of care for the condition?	Azacitidine is licensed as first-line treatment for myelodysplastic syndromes, chronic myelomonocytic leukaemia or acute myeloid leukaemia and would replace best supportive care, low-dose and standard-dose chemotherapy.	2.1
Adverse effects	Common adverse events associated with azacitidine 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.	4.7
Evidence for clinical effectiveness		
Availability, nature and quality of evidence	The Committee noted that the problems relating to loss of patients to follow-up in the pivotal trial (AZA-001) may have introduced bias into the estimates of relative effectiveness, but concluded that this effect was likely to be minimal.	4.5
	The Committee concluded that the estimates of total overall survival compared with conventional care appeared robust.	4.5
	The role of patient preference in the pre-randomisation of the pivotal trial did not affect the way in which the trial results or subsequent	4.6

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	analyses should be considered.	
Relevance to general clinical practice in the NHS	The comparator therapies used in the pivotal trial broadly represented the treatment patients with these conditions receive in the UK.	4.4
Uncertainties generated by the evidence	The small patient numbers limited the precision and certainty of the outcome estimates in the low-dose and standard-dose chemotherapy groups. However the Committee concluded that the estimates of total overall survival compared with conventional care appeared robust.	4.5
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	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 patients receiving conventional care regimens.	3.3
Estimate of the size of the clinical effectiveness including strength of supporting evidence	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.	4.8
Evidence for cost effectiveness		
Availability and nature of evidence	No quality of life data were collected in the pivotal trial, although EORTC data collected in the CALGB 9221 trial suggested improvements in overall health with azacitidine.	4.7
	The use of a weighted average for the comparator was associated with significant methodological limitations. However, taking into account the limitations of the available evidence and in the absence of a satisfactory alternative, the Committee hesitantly concluded that any decision on the cost effectiveness of azacitidine would need to be made using the weighted average.	4.19
	The HMRN registry provided the best available estimate of the proportion of patients receiving each of the conventional care regimens to use	4.20

	in the calculation of the weighted average, namely those patients classified as having IPSS intermediate-2 or high-risk myelodysplastic syndromes.	
Uncertainties around and plausibility of assumptions and inputs in the economic model	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.	4.9
	The Committee concluded that the Weibull distribution generally provided the best overall fit to the Düsseldorf registry long-term survival data.	4.10
	The Committee concluded that it was uncertain whether the utility values used in the model under- or over-estimated the true utility values associated with myelodysplastic syndromes.	4.12
	The Committee noted that the total costs and total QALY gain for azacitidine differed depending on which care regimen it was being compared with. It considered that this variation added to the uncertainty in the model.	4.16
	Because the cost effectiveness of each of the individual conventional care regimens was not established the magnitude and direction of uncertainty in the weighted average ICER was unknown.	4.19
Incorporation of health-related quality of life benefits and utility values	The Committee concluded 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, chronic myelomonocytic leukaemia and acute myeloid leukaemia had been used.	4.11
	The Committee agreed that the utility values provided by MDS UK after the appeal did not provide better estimates of the gains in health-related quality of life than the manufacturer's previous estimates.	4.12
Have any potential significant and substantial health-related benefits been identified that were not included in the	The Committee noted that the model applied constant utility values within each health state, therefore assuming quality of life gains from	4.12

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economic model, and how have they been considered?	the first day of treatment, which it considered unrealistic. The Committee concluded that the utility values used in manufacturer's base case may not have captured the effects of transfusion dependence and fatigue. However, the ICER was only minimally affected by changes in the utility values.	4.11 to 4.13
Are there specific groups of people for whom the technology is particularly cost effective?	No cost-effectiveness evidence was presented for the subgroup of patients with the –7/del(7q) chromosomal abnormality.	4.15
What are the key drivers of cost effectiveness?	The Committee concluded that the ICER estimate was largely driven by the incremental life years gained (that is, the extrapolated survival) and the acquisition cost of azacitidine, and that the ICER was only minimally affected by the changes in health-related quality of life.	4.13
Most likely cost-effectiveness estimate (given as an ICER)	Taking into account the limitations associated with the use of a weighted average and the uncertainty associated with the cost effectiveness of each individual conventional care regimen, the Committee concluded that £47,200 per QALY gained represented the best available estimate of the cost effectiveness of azacitidine.	4.21
Additional factors taken into account		
Patient access schemes (PPRS)	The manufacturer agreed a revised patient access scheme with the Department of Health in January 2011 (which replaces an earlier patient access scheme), in which azacitidine for the treatment of myelodysplastic syndromes, chronic myelomonocytic leukaemia and acute myeloid leukaemia will be available to the NHS with a discount, the level of which is commercial-in-confidence.	2.4
End-of-life considerations	The Committee concluded that azacitidine met the criteria for being a life-extending, end-of-life treatment. The Committee recognised that azacitidine represents an important change in the treatment of patients with myelodysplastic syndromes. The Committee considered that	4.23, 4.24

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	on balance, the additional weight that would need to be assigned to the QALY benefits in this patient group for the cost effectiveness of azacitidine to fall within the current threshold range was acceptable.	
Equalities considerations and social value judgements	The Committee considered whether NICE's duties under the equalities legislation required it to alter or to add to its recommendations in any way. At an earlier meeting, the Committee noted that azacitidine may be of specific benefit to those who, for clinical or religious reasons, are unable to receive blood transfusions, because patients treated with azacitidine require 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 this particular group of patients, or about the effectiveness of azacitidine in this patient population. Therefore the Committee agreed that it would not be appropriate to make recommendations for a subgroup of patients unable to receive blood transfusions. Because the final recommendations (see section 4.24) do not restrict access to azacitidine for any particular group of patients, the Committee concluded that there was now no need to alter or add to its recommendations in any case.	4.25

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5   Implementation

5.1   The Secretary of State and the Welsh Assembly Minister for Health and Social Services have issued directions to the NHS in England and Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends use of a drug or treatment, or other technology, the NHS must usually 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. When there is no NICE technology appraisal guidance on a drug, treatment or other technology, decisions on funding should be made locally.

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/guidance/TAXXX). [NICE to amend list as needed at time of publication]

- Slides highlighting key messages for local discussion.
- Costing template and report to estimate the national and local 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.

5.3   The Department of Health and the manufacturer have agreed that azacitidine will be available to the NHS with a patient access scheme in which a discount is applied to all invoices. The level of

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the discount is confidential. It is the responsibility of the manufacturer to communicate the level of discount to the relevant NHS organisations. Any enquiries from NHS organisations about the patient access scheme can be directed to (company contact to be inserted when guidance is issued).

6 Recommendations for further research

6.1 The Committee recommends that a study estimating utility values 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 2014. 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 2011

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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

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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

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Dr Rosa Legood

Lecturer, London School of Hygiene and Tropical Medicine

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

Dr Peter Norrie

Principal Lecturer in Nursing, DeMontfort University

Professor Stephen Palmer

Professor of Health Economics, 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 Casey Quinn

Lecturer in Health Economics, Division of Primary Care, University of Nottingham

Dr John Rodriguez

Assistant Director of Public Health, NHS Eastern and Coastal Kent

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Mr Alun Roebuck

Consultant Nurse in Critical and Acute Care, United Lincolnshire NHS Trust

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

Professor Rod Taylor

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

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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

Joanne Holden, Bhash Naidoo and Prashanth Kandaswamy

Technical Advisers

Jeremy Powell

Project Manager

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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:

- Edlin R, Connock M, Round J et al. Azacitidine for the treatment of myelodysplastic syndrome, chronic myelomonocytic leukaemia, and acute myeloid leukaemia, April 2009

The Decision Support Unit (DSU) prepared three reports for this appraisal:

- Miners A. DSU report for NICE – Azacitidine STA economic model 09/12/09, December 2009
- Davis S, Wailoo A and Carroll C. Myelodysplastic syndromes – Azacitidine: A critical appraisal of additional evidence submitted by Celgene and the MDS Foundation, September 2010
- Davis S. Myelodysplastic syndromes – Azacitidine: Review of Celgene's response to the post-appeal ACD, December 2010

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

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II   Professional/specialist and patient/carer groups:

- British Committee for Standardisation in Haematology
- British Society for Haematology
- Cancer Research UK
- Leukaemia CARE
- Leukaemia Research Fund
- Leukaemia Society (UK)
- Macmillan Cancer Support
- MDS Patient Support Group
- Rarer Cancers Forum
- Royal College of Nursing
- Royal College of Pathologists
- Royal College of Physicians, Medical Oncology Joint Special Committee
- United Kingdom Oncology Nursing Society

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

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C   The following individuals were selected from clinical specialist and patient expert 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
- Professor Rodney Taylor, nominated by the MDS UK Patient Support Group – patient expert
- Ms Sophie Wintrich, nominated by the MDS UK Patient Support Group – patient expert

D   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