NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final appraisal determination

Lenalidomide for treating myelodysplastic syndromes associated with a deletion 5q cytogenetic abnormality

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

1 Guidance

1.1 Lenalidomide is not recommended within its marketing authorisation, that is, for treating transfusion-dependent anaemia caused by low or intermediate-1 risk myelodysplastic syndromes (MDS) associated with a deletion 5q cytogenetic abnormality when other therapeutic options are insufficient or inadequate.

1.2 People currently receiving lenalidomide that is not recommended for them in NICE guidance should be able to continue treatment until they and their clinician consider it appropriate to stop.

2 The technology

2.1 Lenalidomide (Revlimid, Celgene) is a structural analogue of thalidomide. It has anti-neoplastic, anti-angiogenic, pro-erythropoietic and immunomodulatory properties. Lenalidomide inhibits the proliferation of certain haematopoietic tumour cells, enhances T cell- and natural killer cell-mediated immunity, increases fetal haemoglobin production by CD34+ haematopoietic stem cells and inhibits production of pro-inflammatory cytokines. Lenalidomide has a marketing authorisation 'for the treatment of patients with transfusion-dependent anaemia due to low or

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intermediate-1-risk myelodysplastic syndromes associated with an isolated deletion 5q cytogenetic abnormality when other therapeutic options are insufficient or inadequate'.

2.2   The summary of product characteristics lists the following adverse reactions for lenalidomide: fatigue, neutropenia, constipation, diarrhoea, muscle cramp, anaemia, thrombocytopenia and rash. Lenalidomide is structurally related to thalidomide and there is a risk of teratogenesis. Pregnancy must be ruled out before starting treatment in women of child-bearing age, and these women must use effective contraception while on lenalidomide. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.3   Lenalidomide is available in 21-day packs of 10 mg and 5 mg capsules at net prices of £3780 and £3570 respectively (excluding VAT; 'British national formulary' [BNF] edition 65). The recommended starting dose of lenalidomide is 10 mg orally once daily on days 1 to 21 of repeated 28-day cycles. Dosage is continued or modified based on clinical and laboratory findings. The cost of a 28-day cycle of treatment with 10 mg of lenalidomide (excluding VAT) is £3780. Costs may vary in different settings because of negotiated procurement discounts.

3   The manufacturer's submission

The Appraisal Committee (section 8) considered evidence submitted by the manufacturer of lenalidomide and a review of this submission by the Evidence Review Group (ERG; section 9).

Clinical effectiveness

3.1   The manufacturer performed a systematic review of the evidence on the clinical effectiveness of lenalidomide and comparator

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therapies for patients with low or intermediate-1 risk myelodysplastic syndromes (MDS) associated with a deletion 5q cytogenetic abnormality whose condition is red blood cell transfusion dependent. The review identified a single phase III, randomised, double-blind, placebo-controlled trial (MDS-004), which compared lenalidomide 10 mg (n=69) and lenalidomide 5 mg (n=69) with placebo (n=67). MDS-004 was a multinational study that enrolled patients from 37 study sites including the UK, France, Germany, Italy, Spain, Belgium, Netherlands, Sweden and Israel. The study population comprised adults with MDS whose condition was transfusion dependent and who had International Prognostic Scoring System (IPSS) of low-risk (49%) or intermediate-1 risk (51%) MDS with a deletion 5q cytogenetic abnormality. Patients were stratified according to IPSS karyotype score (0 versus >0; that is, isolated deletion 5q cytogenetic abnormality versus deletion 5q plus 1 or more additional cytogenetic abnormalities). The population specified by the marketing authorisation constituted 76.3% of the total patient population in the MDS-004 study.

3.2   Patients in MDS-004 who had at least a minor erythroid response (that is, a 50% decrease in transfusion requirements) by week 16 of the double-blind phase were eligible to continue double-blind treatment for up to 52 weeks, or until erythroid relapse, disease progression or unacceptable toxicity. Patients receiving placebo or lenalidomide 5 mg who didn't have a minor erythroid response by week 16 could cross over to the lenalidomide 5 mg or 10 mg treatment arms, respectively. Open-label treatment was then continued for up to 156 weeks of total study duration. Patients with disease progression at any time and those randomly assigned to lenalidomide 10 mg without minor erythroid response by week 16 were withdrawn from the study and were ineligible for open-label treatment. The dosage for the 3 treatment arms was lenalidomide

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10 mg per day on days 1 to 21, lenalidomide 5 mg per day on days 1 to 28 and placebo on days 1 to 28 (all 28-day cycles). The manufacturer stated that the dosage of lenalidomide was reduced if dose-limiting toxicities occurred, and complete blood counts were obtained weekly after the development of dose-limiting neutropenia or thrombocytopenia.

3.3   Three study populations were defined in MDS-004: the intention-to-treat (ITT) population, the safety population and the modified-ITT (mITT) population. The ITT population included all randomised patients (n=205). The safety population included all randomised patients who received at least 1 dose of study drug (n=205). The mITT population included patients with low or intermediate-1 risk MDS with deletion 5q and documented red blood cell transfusion dependence, who received at least 1 dose of study drug. Confirmation of deletion 5q status (karyotype analysis) and bone marrow morphology was performed by haematological review after randomisation. Therefore some patients not fulfilling the inclusion criteria were included in the ITT population. For the mITT population, 76.3% of patients had an isolated deletion 5q cytogenetic abnormality and 23.7% had deletion 5q plus one or more additional cytogenetic abnormalities. The baseline characteristics of the patients in the treatment arms for the mITT population were similar.

3.4   The primary end point of the MDS-004 trial was transfusion independence lasting for at least 26 consecutive weeks. Secondary end points included erythroid response at 16 weeks, duration of red blood cell transfusion independence, cytogenetic response at weeks 12, 24 and every 24 weeks thereafter, overall survival, progression to acute myeloid leukaemia (AML) and safety. Health-related quality of life was assessed using the Functional

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Assessment of Cancer Therapy-Anaemia (FACT-An) questionnaire at weeks 12, 24, 36 and 48.

3.5   For the double-blind phase of MDS-004, statistically significantly more patients in the mITT population were transfusion independent for at least 26 weeks (the primary end point) with lenalidomide 10 mg (56.1%) and 5 mg (42.6%) than with placebo (5.9%; $p<0.001$ compared with both lenalidomide groups). Using the International Working Group (IWG) 2000 and 2006 criteria for erythroid response, transfusion independence rates for at least 8 weeks in the mITT population were also statistically significantly higher for the lenalidomide 5 mg and 10 mg treatment groups compared with placebo. Similar results were obtained for the ITT population. Median duration of transfusion independence of at least 8 weeks was not reached in the lenalidomide 5 mg or 10 mg treatment groups.

3.6   In the safety population, median time to progression to AML (from date of randomisation to progression to AML, death, or last known contact for people without AML, which ever was earliest) was 30.9 months (range 2.1–56.5 months) in the placebo group, 36.1 months (range 0.4–57.7 months) in the lenalidomide 10 mg group and 31.8 months (range 0.8–59.4 months) in the lenalidomide 5 mg group. Before crossover at 16 weeks, 2 patients (3.0%) in the placebo group, 0 in the lenalidomide 10 mg group and 2 (2.9%) in the lenalidomide 5 mg group had progressed to AML. Overall, 52 patients (25.4%) progressed to AML during the double-blind and open-label phases. The cumulative risk of AML for the lenalidomide 5 mg and 10 mg groups combined was 16.8% (95% CI 9.8–23.7) at 2 years and 25.1% (95% CI 17.1–33.1) at 3 years.

3.7   The median duration of overall survival follow-up in the safety population was 35.9 months (range 2.1–56.5 months) in the

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placebo group, 36.9 months (range 0.4–57.7 months) in the lenalidomide 10 mg group and 35.5 months (range 1.9–59.4 months) in the lenalidomide 5 mg group. Based on Kaplan-Meier curves, the median length of overall survival was 42.4 months in the lenalidomide 10 mg group (95% CI 31.9 to not reached), at least 35.5 months in the 5 mg group (95% CI 24.6 to not reached), and 44.5 months (95% CI 35.5 to not reached) in the placebo group. The manufacturer stated that overall survival was similar between patients included in and excluded from the mITT population (p=0.9218).The manufacturer did not adjust the overall survival results using formal statistical methods for any treatment crossover that occurred.

3.8   In MDS-004, cytogenetic response was assessed using IWG 2000 criteria. Cytogenetic response (complete plus partial) rates in the mITT population were 50% in the lenalidomide 10 mg group and 25% in the 5 mg group, respectively. No cytogenetic responses occurred in the placebo group (p<0.001 compared with both lenalidomide groups). Cytogenetic progression (development of new independent clones as well as additional aberrations together with deletion 5q) was observed in 23.5% of patients treated with lenalidomide 10 mg (p=0.50 compared with placebo), 31.3% in patients treated with lenalidomide 5 mg (p=0.17 compared with placebo), and 14.3% of patients receiving placebo. Similar results were observed in the ITT population. Median time to cytogenetic progression was 93 days (range 85–170 days) in the lenalidomide 10 mg group, 85 days (range 83–339 days) in the lenalidomide 5 mg group, and 99 days (range 83–172 days) in the placebo group.

3.9   Health-related quality of life data were collected for 167 patients in MDS-004 using the FACT-An questionnaire. Baseline and week

12 (that is, before crossover) FACT-An scores were available for 71% of randomly assigned patients (lenalidomide 10 mg, n=48; 5 mg, n=45; placebo, n=52). Mean change in FACT-An scores from baseline to week 12 was statistically significantly higher in the lenalidomide 10 mg (5.8; $p<0.05$) and 5 mg (5.9 versus; $p<0.05$) groups than in the placebo group (−2.5).

3.10   The manufacturer reported adverse event rates for the double-blind safety population in MDS-004. A higher proportion of patients in the lenalidomide 10 mg (95.7%) and 5 mg groups (98.6%) had at least 1 drug-related adverse event compared with the placebo group (49.3%). The most frequently reported drug-related adverse events were neutropenia (14.9% in the placebo group, and 75.4% in each of the lenalidomide groups) and thrombocytopenia (3.0% in the placebo group, 39.1% in the lenalidomide 5 mg group and 47.8% in the lenalidomide 10 mg group). For serious infections, only rates of grade 3 or 4 pneumonia were reported by the manufacturer (1.5% in the placebo group, 1.4% in the lenalidomide 5 mg group and 4.3% in the lenalidomide 10 mg group).

3.11   The manufacturer developed a de novo Markov state-transition cost–utility model which simulated cohorts of patients with low to intermediate-1 risk MDS with deletion 5q receiving lenalidomide 10 mg or best supportive care. The model cycle length was 4 weeks to reflect the dosing interval for lenalidomide treatment and a half-cycle correction was not applied. The time horizon of the model was 20 years based on an average patient age of 67 years in the MDS-004 study. An NHS and personal social services perspective was taken and costs and benefits were discounted at 3.5%.

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3.12   The model structure was developed to reflect 3 key features of MDS deletion 5q treatment:

- whether the patient was transfusion dependent or independent
- whether the patient needed iron chelation after a certain number of red blood cell transfusions
- whether the patient's condition progressed to AML.

After starting treatment, patients moved to 3 possible health states relating to transfusion status: transfusion independent and transfusion dependent with or without chelation. Additional states were defined to reflect response to iron chelation and potential hepatic and diabetic complications, and increased risk of cardiac disease caused by red blood cell transfusion. In addition, patients who were transfusion dependent or independent with or without complications could develop AML. This resulted in a total of 14 possible health states in the model including death.

3.13   Clinical-effectiveness data from the ITT population in the MDS-004 study were used in the model. The manufacturer stated that this population more closely matched the NICE scope than the mITT population. It also stated that using the mITT population substantially reduced the amount of available data and that, in this population, no statistically significant differences were observed in key end points between trial arms in MDS-004. The dosing schedule for patients treated with lenalidomide 10 mg was also based on the MDS-004 study, in which patients received 21 days of continuous treatment every 28 days. The manufacturer assumed that patients in the lenalidomide group remained on treatment until their condition stopped responding to treatment, that is, they became transfusion dependent. Best supportive care was based on the placebo arm of the MDS-004 study, which included the

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provision of blood transfusions for transfusion-dependent patients. The manufacturer stated that, in UK clinical practice, best supportive care may also include an erythropoiesis stimulating agent (ESA). Therefore, the manufacturer assumed that 28% of patients in the best supportive care group received an ESA for 3 cycles on the basis of the proportion of UK patients in MDS-004 who received an ESA before the trial started. In addition, it was assumed that patients whose condition did not respond to an ESA as part of best supportive care would receive an additional granulocyte colony-stimulating factor (G-CSF) for 3 cycles.

3.14   In the model, treatment response was defined as patients becoming independent of transfusions. The proportion of patients who became transfusion independent for 56 consecutive days (based on IWG 2000 criteria) was 60.9% for the lenalidomide group and 7.5% for the best supportive care group. The response rates of 21.7% for patients who received an ESA and a G-CSF in the best supportive care group were taken from a separate study that reported response rates after combination therapy (Jadersten et al. 2005). However, the manufacturer stated that this was unlikely to be representative of ESA and G-CSF use in the UK because combination therapy is started after the failure of ESA monotherapy. On the basis of a separate study by Balleari et al. (2006), the manufacturer assumed that response rates to monotherapy with either ESA or a G-CSF would be half of those to combination therapy, resulting in response rates of 10.8% for ESA monotherapy and G-CSF.

3.15   The duration of response to treatment with lenalidomide and best supportive care in the model was based on patient-level data taken from the MDS-004 ITT population. Because patient crossover was permitted in MDS-004, the manufacturer used log-rank tests to

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determine whether there was a significant difference in response duration according to whether a treatment was provided as first- or second-line treatment in the study. The manufacturer stated that the results showed that the order in which patients received treatment in MDS-004 did not have a significant impact on duration of response. Parametric response duration curves were fitted to patients in the lenalidomide 10 mg treatment arm in MDS-004 to estimate response duration in the lenalidomide group. The manufacturer stated that response duration curves could not be estimated for patients in the placebo arm because of insufficient numbers of patients (n=5) whose condition responded to treatment. Therefore, the manufacturer used data from the lenalidomide 5 mg treatment arm in MDS-004 to approximate duration of response to best supportive care. Based on goodness-of-fit tests using the Integrated Brier Score and Akaike Information Criterion, the log-normal distribution was fitted to both response duration curves.

3.16   The manufacturer assumed that patients in the transfusion-dependent states in the model received red blood cell and platelet transfusions. On the basis of data from MDS-004, it was assumed that patients needed an average of 1.89 red blood cell transfusions to provide 4.57 red blood cell units and an average of 0.02 platelet transfusions to provide 0.06 platelet units per 28-day cycle. The manufacturer also assumed that patients who were transfusion dependent had an increased risk of cardiac disease, which was based on the findings of a study by Malcovati et al. (2011). A Gompertz curve was fitted to data from this study to estimate the probability of transfusion-dependent patients who progressed to cardiac disease.

3.17   The manufacturer assumed that patients who were transfusion dependent started iron chelation therapy to avoid complications

associated with iron overload. It was assumed that patients started iron chelation therapy when they reached a threshold of 25 red blood cell units. The manufacturer also assumed that patients had already received 9.15 red blood cell units per 8 weeks on the basis of the average number of units that patients had received before entering the MDS-004 study. A response rate for iron chelation of 66% was taken from a study by Kontoghiorges et al. (2000) and was assumed to occur in the first cycle of treatment. Patients who needed iron chelation moved to either the chelation or chelation failure state. The manufacturer assumed that patients whose disease responded to treatment continued to receive iron chelation until progression to AML or death. Patients in the model whose disease did not respond to iron chelation therapy were assumed to be at risk of iron overload complications, including diabetes mellitus and hepatic complications. The probabilities of developing diabetes mellitus (0.21%) and hepatic complications (0.66%) per 28-day cycle on iron chelation were taken from a study by Jaeger et al. (2008).

3.18   The manufacturer stated that survival of patients with MDS is strongly related to transfusion dependence. Therefore, data from the MDS-004 study were used to estimate separate mortality curves for patients who were transfusion dependent or independent at 8 weeks. Based on goodness-of-fit, the Weibull distribution was fitted to data from MDS-004. The manufacturer stated that crossover of patients in the MDS-004 study at week 16 precluded any long-term assessment of the impact of lenalidomide on survival and, as a result, using only MDS-004 study data was likely to result in an underestimate of overall survival. Therefore, the median survival for best supportive care in the model was adjusted to match the combined median survival data reported from a phase II

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trial, MDS-003, and the phase III MDS-004 study, resulting in a figure of 3.8 years.

3.19   Patients in the model were assumed to be at risk of developing AML. The time to progression to AML was taken from an individual patient-level analysis from the MDS-004 study and was estimated separately for transfusion-dependent and independent patients. On the basis of goodness-of-fit, the Weibull distribution was chosen to estimate time to AML progression curves. AML-related mortality could not be estimated from the MDS-004 study because the number of patients who died from AML was too low. Therefore, the manufacturer used data from a study by Wahlin et al. (2001) of elderly patients with AML, including 113 patients with MDS caused by deletion 5q. Although the log-normal function provided the best fit to the data from this study, it also resulted in a 'long tail' whereby some patients remained alive for an unrealistically long time. A Weibull distribution was therefore chosen to estimate the survival time for patients who developed AML in the model because it did not result in such a 'long tail'.

3.20   The manufacturer included grade 3 or 4 neutropenia and thrombocytopenia episodes in the model, because of differences in these adverse events between the placebo and lenalidomide treatment arms in MDS-004. The manufacturer stated that it was unlikely that all neutropenia and thrombocytopenia events could be attributed to lenalidomide treatment because MDS is characterised by these peripheral cytopenias. Therefore, the number of patients who had neutropenia and thrombocytopenia in the lenalidomide group was adjusted by subtracting the patients who had these events in the placebo group. The manufacturer assumed that any adverse events in the lenalidomide group occurred only in the first 4 cycles of the model. On the basis of data from MDS-004, the

manufacturer assumed that only a proportion of patients who had neutropenia (27.7%) and thrombocytopenia (6%) needed additional treatment. The manufacturer did not include other adverse events such as deep vein thrombosis or pulmonary embolism in the model because of the low incidence of these events in MDS-004.

3.21   The model accounted for 2 periods of treatment interruption during which patients in the lenalidomide group did not receive treatment. On the basis of data from the MDS-004 ITT population, it was assumed that 68.7% of patients in the lenalidomide group had a first dose interruption and 73.8% had a second dose interruption. The mean time to first treatment interruption was 54.2 days and the length of treatment interruption was 17.5 days. After the first dose interruption, patients in the lenalidomide group resumed treatment at a lower dose of 5 mg for 28 days per cycle. The mean time to second treatment interruption (from the start of the first interruption) was 72.1 days and the length of interruption was 13.9 days. After the second dose interruption, patients in the lenalidomide group resumed treatment at a lower dose of 5 mg for 14 days per cycle. The cost of lenalidomide treatment was adjusted to take these treatment interruptions into consideration but the manufacturer stated that there was no need for clinical outcomes to be adjusted in a similar way, because the efficacy data for the ITT population used in the model already accounted for these interruptions.

3.22   The MDS-004 trial assessed health-related quality of life using the EQ-5D at baseline, and the FACT-An questionnaire at baseline and at weeks 12, 24, 36 and 48. The manufacturer conducted preliminary analyses to explore any relationship between EQ-5D utility values and the FACT-An. However, regression models to map FACT-An scores from MDS-004 to EQ-5D utility values resulted in an unacceptable level of error. Therefore, the

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manufacturer performed a systematic literature search to identify relevant health-related quality of life data for patients with MDS. A total of 4 potentially relevant studies were identified (Buckstein et al. 2009 and 2011, Goss et al. 2006 and Szende et al. 2009). The manufacturer chose to use Szende et al. (2009). In this study, utility data were collected from a sample of 47 MDS patients of mean age 67 years (including 21 from the UK) using visual analogue scale and time trade-off methods. Patients were interviewed to elicit utility values for 3 health states: transfusion independence, reduced transfusion and transfusion dependence. The resulting mean utility values for the UK sample using the time trade-off method were 0.85 for transfusion independence and 0.65 for transfusion dependence. The study did not estimate utility values for the AML state, so the manufacturer assumed that patients in the AML state had the same utility value for transfusion dependence of 0.65. Utility values in the model were adjusted by an age-dependent factor taken from Kind et al. (1999). The studies by Buckstein et al. reported EQ-5D utility values for 69 Canadian patients (mean age 73 years) with MDS, resulting in utility values of 0.80 for transfusion independence and 0.63 for transfusion dependence. The study by Goss et al. (2006) reported utility values estimated using the time trade-off technique in 8 US patients with low and intermediate-1 risk MDS, resulting in utility values of 0.91 for transfusion independence and 0.50 for transfusion dependence. The utility values from both of these studies were used in additional scenario analyses conducted by the manufacturer.

3.23   Utility decrements associated with iron chelation therapy (21% for intravenous iron chelation and 0% for oral chelation) were obtained from a study by McLeod (2009). Utility decrements for adverse events, including cardiac disease (17.9%), diabetes (12.3%) and hepatic complications (8.0%) were obtained from studies by

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Fryback (1993) and Wong (1995). The model did not incorporate utility decrements for patients who had neutropenia and thrombocytopenia episodes. The manufacturer's justification was that these adverse events were likely to have a short-term effect on quality of life.

3.24   The manufacturer's model included drug acquisition, monitoring costs and costs of adverse events. The acquisition costs of lenalidomide were based on the dosing observed in the MDS-004 trial, which included dose interruption because of adverse events. The costs of ESA (£885 per cycle) and G-CSF (£633 per cycle) were also included for 28% of patients in the best supportive care group. Drug acquisition prices were obtained from the BNF 64. In addition, monitoring costs (including GP visits and blood tests) and transfusion costs (including administration and acquisition of red blood cell and platelet units) were included. The costs of treating AML (£1919.40 per cycle) were taken from [Azacitidine for the treatment of myelodysplastic syndromes, chronic myelomonocytic leukaemia and acute myeloid leukaemia](#) (NICE technology appraisal guidance 218). The costs of thrombocytopenia and neutropenia episodes of £1636.38 were taken from NHS reference costs 2011/12. The model also included the annual costs of iron chelation and transfusion-dependent complications, which were taken from the literature. To estimate the costs of iron chelation therapy, the manufacturer assumed that patients had either intravenous desferrioxamine (29%) or oral deferasirox (71%) based on prescription cost analysis data for England (2010), resulting in a total cost of £1383.39 per cycle. The frequency of monitoring associated with lenalidomide treatment was taken directly from the summary of product characteristics: GP visits (and blood counts) occurred weekly for the first 8 weeks, bi-weekly for the next 4 weeks and then 4-weekly thereafter. For best

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supportive care, monitoring was assumed to occur once every 4 weeks throughout treatment.

3.25   The clinical outcomes from the manufacturer's model resulted in total undiscounted life years in the lenalidomide and best supportive care groups of 5.69 years and 4.53 years respectively. The manufacturer's base-case deterministic cost-effectiveness analysis resulted in an incremental cost-effectiveness ratio (ICER) of £56,965 per quality-adjusted life year (QALY) gained for lenalidomide compared with best supportive care (incremental costs £50,582 and incremental QALYs 0.89). The probabilistic cost-effectiveness analysis resulted in an ICER of £58,178 per QALY gained.

3.26   The manufacturer undertook a series of deterministic sensitivity analyses on various model parameters. The cost-effectiveness estimate of lenalidomide compared with best supportive care was most sensitive to the utility value for the transfusion-independent state. The ICER was also sensitive to the response rate for the lenalidomide treatment group and the utility value for the transfusion-dependent state. The manufacturer also conducted a range of scenario analyses, which included altering the population used to estimate the model parameters, altering the proportion of patients in the best supportive care group who received an ESA, altering the number of red blood cell units patients received before iron chelation therapy was started, using alternative utility values from the studies by Goss and Buckstein and using alternative methods of extrapolating response duration, AML progression and overall survival. The ICERs were robust to nearly all of the scenarios explored. However, when the manufacturer applied alternative utility values for the transfusion-independent (0.91), transfusion-dependent (0.5) and AML (0.5) states taken from the

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study by Goss et al. (2006), this resulted in an ICER of £47,621 per QALY gained. Results of the probabilistic sensitivity analysis showed that at £30,000 per QALY gained, lenalidomide had a 0% probability of being cost effective.

Evidence Review Group comments

3.27   The ERG considered that the manufacturer had identified all the available evidence on the clinical effectiveness of lenalidomide for treating myelodysplastic syndromes associated with the deletion 5q cytogenetic abnormality. The ERG noted that a significant proportion of patients in the lenalidomide 5 mg and 10 mg groups had an adverse event resulting in dose interruption or reduction. It also noted that dose reductions made it difficult to distinguish between the 5 mg and 10 mg lenalidomide treatment groups. It noted that because patients in the placebo or lenalidomide 5 mg groups without minor erythroid response by week 16 or those with erythroid relapse could cross over, only 1 patient in the placebo group completed the 52-week double-blind phase. The ERG suggested that one of the main concerns for patients treated with lenalidomide is the incidence of increased clonal evolution and progression to AML. The ERG was concerned that because patients were able to switch from placebo to active drug treatment in the MDS-004 study, the chances of detecting prolonged survival or acceleration of leukaemia progression were limited. Overall, the ERG considered that that assessment of the long-term effectiveness of lenalidomide was compromised because patients in the MDS-004 study were allowed to switch treatment after 16 weeks.

3.28   The ERG noted that data were reported separately for 2 populations in the MDS-004 study: the ITT and mITT population,

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although not all results were reported for both populations. The ERG also noted that confirmation of deletion 5q status (by karyotype analysis) and bone marrow morphology were performed by central haematological review after randomisation, resulting in patients whose disease did not meet the study inclusion criteria being included in the ITT population. The ERG noted that it was not clear how differences between these 2 populations could influence the results.

3.29   The ERG stated that the manufacturer's economic model was generally well presented and reported. However, the ERG noted that the model described in the manufacturer's submission did not fully correspond with the model structure in the electronic model provided. It also noted that the manufacturer did not consider progression to intermediate-2 or high-risk MDS in the model because such data were not collected in MDS-004. The ERG considered that it would have been more reasonable for a lifetime model to incorporate all future costs and effects, including the possibility of disease progression and reduced transfusion burden. The ERG disagreed with the manufacturer's decision not to apply a half-cycle correction in the model because of the short cycle length of 28 days. The ERG considered that short cycles would involve small changes between 2 consecutive cycles. The ERG noted that the cycles at the start of the model showed a significant redistribution between the various health states, suggesting that a cycle of 28 days was rather long during this phase of the model.

3.30   The ERG noted that in the manufacturer's economic model, best supportive care was defined as blood transfusions for transfusion-dependent patients. No changes to best supportive care (in terms of transfusion frequency or iron chelation therapy) were assumed when cardiac conditions, diabetes, or hepatic conditions occurred.

The ERG considered that it was unclear whether best supportive care as represented in the model was similar enough to actual patient experience in England and Wales.

3.31   The ERG considered the response rates used in the manufacturer's model, which were based on the MDS-004 ITT population. The ERG noted that the manufacturer's description of the model stated that response to treatment was assumed to occur within the first cycle, so that all patients spent the first cycle in the transfusion-dependent state. However, the ERG noted that the model started with the results of the treatment initiation and that patients moved immediately from the first cycle onwards to the transfusion-independent state. The ERG considered that this assumption may have been optimistic because the overall response rate also included patients whose condition did not respond immediately to treatment. In response to clarification, the manufacturer provided data on the proportion of patients responding to treatment according to 28-day cycles in the MDS-004 study, which showed that the lenalidomide 10 mg arm had a response rate of 60.9% after 112 days and the placebo arm had a response rate of 7.5% after 182 days. The ERG considered that it would have been more appropriate to use these data rather than assuming that all patients whose condition responded to treatment were transfusion independent from cycle 1 onwards.

3.32   The ERG noted that neither the proportion of patients receiving ESA as part of best supportive care nor the response rate to ESA could be obtained from the MDS-004 trial, which introduced additional uncertainty in the model. It noted that, according to expert opinion given to the ERG, there is some uncertainty about the effect of providing ESA to patients with MDS with deletion 5q. The ERG also noted that the initial response rates to best

supportive care in the model were weighted twice by the proportion of patients (28%) who received ESA and G-CSF therapy. In response to clarification, the manufacturer confirmed that these were programming errors. The ERG considered that, in the absence of other available data, it was appropriate for the manufacturer to assume that response duration for the best supportive care group could be estimated from the lenalidomide 5 mg treatment arm in MDS-004. However, it also considered that the manufacturer's rationale for using response duration estimates from the lenalidomide 5 mg arm rather than the 10 mg arm seemed arbitrary.

3.33   The ERG noted that the cost effectiveness of lenalidomide was sensitive to the proportion of patients in the lenalidomide treatment group who had a second dose interruption in the model. The ERG noted that these values were directly obtained from the MDS-004 trial, but that only cost estimates were assumed to be affected by treatment interruptions in the model, and the clinical effectiveness of lenalidomide was unaffected. The ERG suggested that, in clinical practice, treatment interruptions would affect the response rates to lenalidomide treatment. The ERG also noted that the programming of dose interruptions in the electronic model contained errors.

3.34   The ERG noted that patients in the transfusion-dependent state in the model started iron chelation therapy after receiving 25 units of red blood cells and that at the start of the model they were assumed to have already received an average of 9.15 red blood cell units over 8 weeks, on the basis of data from MDS-004. However, the ERG noted that the manufacturer had multiplied the number of red blood cell units that patients had received at the start of the model by 2, which resulted in patients in the transfusion-

dependent state needing iron chelation therapy after 8 weeks in the model instead of 16 weeks. The ERG therefore conducted an exploratory scenario analysis assuming that patients in the transfusion dependent state would start iron chelation therapy after 8 weeks.

3.35   The ERG noted that all patients in the model would be monitored by a GP. In response to clarification, the manufacturer stated that the cost of haematology visits were included in the costs of transfusion dependence and associated adverse events and that, as a result, haematology visits were not included as part of regular patient monitoring in the model. However, the ERG considered that because most patients in the model were not treated for adverse events, it would be more reasonable for patients to be monitored by a haematologist rather than a GP. The ERG therefore conducted an exploratory scenario analysis assuming that all monitoring would take place at a haematologist visit.

3.36   The ERG noted that the utility values taken from the study by Szende et al. (2009) did not conform to the NICE reference case because they were obtained from a sample of UK patients with MDS rather than a sample of the UK population. The ERG considered that the health state descriptions in the Szende et al. (2009) study were very broad, and therefore the transfusion-dependent state may have already incorporated some of the adverse events associated with chelation therapy or complications such as cardiac disease, diabetes or hepatic complications. The ERG noted that using a utility value of 0.65 for patients in the transfusion-dependent state may favour lenalidomide because patients in the best supportive care group spent a much longer time in this health state, thus increasing the QALY difference between lenalidomide and best supportive care in the model. The ERG also

considered that the manufacturer's assumption that utility values in the AML state would be the same as those for the transfusion-dependent state was questionable. However, the ERG noted that because there was no difference between the 2 treatment groups in the time spent in the AML state, the impact of the utility value for the AML state was negligible. The ERG also noted that the manufacturer did not apply utility decrements for neutropenia and thrombocytopenia events associated with lenalidomide treatment, although it accepted that the impact of these events on health-related quality of life was likely to be small.

3.37   The ERG identified several issues in relation to the resource use and cost estimates used in the manufacturer's model. The ERG noted that patients receiving iron chelation therapy in the model either had intravenous desferrioxamine or oral deferasirox treatment based on prescription cost analysis data in England from 2010. The ERG considered that deferiprone, which is a third possible iron chelation therapy listed in the prescription cost analysis, should also have been included. When the ERG included deferiprone and adjusted the proportion of patients who were treated with the 3 iron chelation therapies based on 2011 prescription cost analysis data, this reduced the total cost of iron chelation therapy from £1383 to £1332 per 28-day cycle. The ERG noted that the manufacturer's estimated cost of AML treatment of £1919.40 was based on a 5-week cycle rather than a 4-week cycle used in the model. The ERG also identified alternative cost estimates for episodes of neutropenia (£1045) and thrombocytopenia (£1768) from the NHS reference costs (2011/12). The ERG considered that the manufacturer's assumption of standard errors of 10% of the mean cost estimates for complications and adverse events used in the probabilistic sensitivity analysis were too small and that standard errors of 20%

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of the mean estimate would be more reasonable. Similarly, the ERG noted that the manufacturer's probabilistic sensitivity analysis did not account for uncertainty around the number of monitoring visits in both treatment groups.

3.38   The ERG re-ran the manufacturer's model incorporating the following adjustments:

- Programming errors confirmed by the manufacturer were removed.
- Programming errors for dose interruptions and days on active treatment in the model were removed.
- A half-cycle correction was included.
- Costs of iron chelation therapy were updated to £1332 per cycle to include deferiprone.
- Treatment costs of AML were amended to £1451 per 28 day cycle.
- Response was distributed over time according to the trial instead of all patients from cycle 1 onwards.
- Costs of neutropenia and thrombocytopenia were amended to £1045 and £1768 respectively.
- Uncertainty around the number of monitoring visits, and increased uncertainty around cost estimates, complications, and adverse events were incorporated into the model.

3.39   When the ERG included all of these changes in the manufacturer's model the deterministic cost-effectiveness analysis resulted in an ICER of £62,674 per QALY gained for lenalidomide compared with best supportive care (incremental costs £50,898 and incremental QALYs 0.81). The corresponding probabilistic cost-effectiveness analysis resulted in an ICER of £65,052 per QALY gained.

3.40   The ERG reproduced the manufacturer's sensitivity and scenario analyses in the amended model. The sensitivity analyses found that the cost effectiveness of lenalidomide compared with best supportive care was most sensitive to the utility values for the transfusion-independent state and the response rate for the lenalidomide treatment group. When the ERG re-ran the manufacturer's scenario analyses, the ICERs were robust to nearly all of the scenarios explored (see 3.26) except when alternative utility values taken from the study by Goss et al. (2006) were used, which resulted in an ICER of £51,956 per QALY gained.

3.41   The ERG undertook an additional series of scenario analyses. The scenarios which had the most substantial effect on the ICER were the utility value for transition dependence and the proportion of patients who received intravenous iron chelation therapy. When the utility value for transfusion dependence was increased from 0.65 to 0.77 (the value for reduced transfusion burden taken from Szende et al. [2009]), the resulting ICER was £68,357 per QALY gained. When the proportion of patients who received intravenous iron chelation therapy was increased from 5.7% to 100%, the resulting ICER was £56,750 per QALY gained. If it was assumed that patients in the transfusion-dependent state would start iron chelation therapy after 4 cycles, the ICER was £67,428 per QALY gained. If it was assumed that all monitoring would take place at a haematologist visit, the ICER was £64,079 per QALY gained.

Manufacturer's response to consultation

3.42   The manufacturer submitted the results of a systematic literature review to support its rationale that transfusion dependence is a prognostic factor for overall survival and rate of progression to AML. Sixteen of the 17 studies (mainly retrospective case series or

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registry populations, also one study describing the results of a randomised controlled trial and one post-hoc analysis of randomised controlled trial data – 5000 patients in total) meeting the inclusion criteria reported statistically significant associations between transfusion status and overall survival. This association was explained by:

- transfusion dependence and anaemia leading to increased non-leukaemic death (particularly cardiac death)
- transfusion dependence and anaemia leading to increased risk of AML and leukaemic death
- transfusion independence after dependency at baseline improving overall survival because of reduced complications from chronic anaemia.

The manufacturer also cited literature that examined the relationship between AML and both transfusion status and erythroid response, arguing that lenalidomide triggers programmed cell death in the deletion (5q) clone, and that the MDS-004 trial showed significant reductions in progression to AML for patients whose condition responded to lenalidomide.

3.43   In response to the appraisal consultation document, the manufacturer revised the economic model. It accepted the adjustments described in sections 3.38 and 3.39, which increased the base-case ICER to £62,674. It also accepted that monitoring would be undertaken by a GP rather than a haematologist, further raising the base-case ICER to £65,153. A model scenario was then implemented that removed any benefit of lenalidomide on progression to AML. This again increased the base-case ICER to £68,125. However, the manufacturer argued that this scenario was not appropriate, because it ignored the literature they had identified showing that transfusion dependence is an important prognostic

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factor for AML. The manufacturer also provided further information to explain a labelling error in their model about iron chelation. It outlined that the underlying model was accurate for the assumption of when iron chelation started, despite this labelling error, and that no adjustments in the base-case ICER were therefore needed. Finally, the manufacturer submitted their methods for attempting to map FACT-An scores to EQ-5D and the way they accounted for crossover.

3.44   The ERG considered the additional information submitted by the manufacturer. It agreed that this information, combined with the results of the MDS-004 trial, suggested that it was reasonable to assume a 2-step relationship, first between lenalidomide response and transfusion independence, and then transfusion independence and overall survival. However, there was still some uncertainty in the strength of the relationship beyond 5 years. For AML progression, the ERG outlined differing evidence from the MDS-004 trial. While Kaplan Meier survival curves showed significant differences in progression to AML in favour of those whose disease responded to lenalidomide, a univariate Cox-regression of time to AML showed that response status was not a significant variable. The ERG also reviewed the economic model, agreeing with the change in monitoring costs, and noting that that revision for iron chelation was unnecessary because of the labelling error. They noted that the manufacturer had not included a half-cycle correction, which reduced the ICER to £64,079 and that this ICER was deterministic.

3.45   Full details of all the evidence are in the manufacturer's submission and the ERG report.

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4 Consideration of the evidence

The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of lenalidomide, having considered evidence on the nature of myelodysplastic syndromes (MDS) associated with a deletion 5q cytogenetic abnormality and the value placed on the benefits of lenalidomide by people with the condition, those who represent them, and clinical specialists. It also took into account the effective use of NHS resources.

4.1   The Committee considered the treatment pathway in the UK for people with MDS associated with a deletion 5q cytogenetic abnormality, taking into account the marketing authorisation for lenalidomide (for treating transfusion-dependent anaemia caused by low or intermediate-1 risk MDS associated with a deletion 5q cytogenetic abnormality when other therapeutic options are insufficient or inadequate). It noted that the comparator listed in the NICE scope was best supportive care including blood transfusions for people with intermediate-1 or low-risk MDS. The Committee also noted that [Azacitidine for the treatment of myelodysplastic syndromes, chronic myelomonocytic leukaemia and acute myeloid leukaemia](#) (NICE technology appraisal guidance 218) recommends azacitidine as a treatment option for patients with intermediate-2 or high-risk MDS (a different International Prognostic Scoring System [IPSS] risk category than this appraisal) who are not eligible for haematopoietic stem cell transplantation. It heard from the clinical specialist that the main treatment option currently available for people with MDS associated with a deletion 5q cytogenetic abnormality is best supportive care, which involves regular red blood cell transfusions, and that low-dose standard chemotherapy or immunosuppressive therapies are used for some patients. The clinical specialist also stated that a small proportion of people

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would also receive an erythropoiesis stimulating agent (ESA) as part of best supportive care and that iron chelation therapy is used to avoid longer-term complications associated with transfusion. The clinical specialist also stated that thalidomide may be useful for some people with MDS associated with a deletion 5q cytogenetic abnormality although its side effects mean that it is rarely used in UK clinical practice.

4.2   The Committee heard from the clinical specialist that lenalidomide is an effective targeted therapy with a real impact on the need for blood transfusions. The patient experts agreed that this was a major benefit, with reduced fatigue significantly improving quality of life. They highlighted that the need to have regular blood transfusions and blood tests at hospital is both inconvenient, because it needs regular time off work and usual activities, and demoralising because the person is constantly reminded of their disease. The patient experts suggested that lenalidomide, by contrast, is a convenient, effective oral drug that would reduce the need for blood transfusions. The Committee recognised the need for alternative treatment options that would significantly reduce blood transfusion dependence in people with MDS associated with a deletion 5q cytogenetic abnormality, and it took this into consideration when making its decision.

4.3   The Committee discussed the decision problem as presented in the manufacturer's submission. It noted that the manufacturer did not include azacitidine or stem cell transplantation as comparators because the population in its submission did not include patients with intermediate-2 and high-risk MDS. The Committee accepted that azacitidine or stem cell transplantation would not be used in clinical practice to treat people with intermediate-1 or low-risk MDS. Therefore, the Committee agreed that, as defined in the scope,

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best supportive care was the appropriate comparator for lenalidomide in people with intermediate-1 or low-risk MDS.

Clinical effectiveness

4.4   The Committee discussed the clinical effectiveness of lenalidomide in people with MDS associated with a deletion 5q cytogenetic abnormality. It noted that the evidence presented by the manufacturer was taken primarily from the MDS-004 study, which recruited people with low or intermediate-1 risk MDS associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities. It also noted that this study included a broader range of people than that specified in the marketing authorisation for lenalidomide, which includes people with transfusion-dependent anaemia due to low or intermediate-1 risk MDS associated with an isolated deletion 5q cytogenetic abnormality when other therapeutic options are insufficient or inadequate. However, the Committee was aware that a significant proportion of the people in the MDS-004 study were covered by the marketing authorisation. It concluded that it would be able to consider all of the evidence in the MDS-004 study when making recommendations on lenalidomide for treating MDS associated with a deletion 5q cytogenetic abnormality.

4.5   The Committee considered the results of the MDS-004 study. It noted that the rates of transfusion independence and improvements in health-related quality of life as measured by the Functional Assessment of Cancer Therapy-Anaemia (FACT-An) questionnaire were significantly better in people treated with lenalidomide (see sections 3.5 and 3.9). The Committee concluded that, on the basis of the evidence on transfusion independence and health-related quality of life, lenalidomide is a clinically effective

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treatment for people with MDS associated with a deletion 5q cytogenetic abnormality.

4.6   The Committee went on to discuss the overall survival of people treated with and without lenalidomide, noting that overall survival for the placebo and lenalidomide groups was greater than 35 months. The Committee noted that there was no statistically significant difference in overall survival between the lenalidomide and placebo treatment groups in the MDS-004 study. It was aware that patients in the placebo arm were permitted to cross over to lenalidomide treatment after 16 weeks (see section 3.2). The Committee heard from the manufacturer that it did not consider it appropriate to use statistical approaches to adjust for this crossover because it occurred too early in the study to permit a reliable estimate of survival for the placebo arm. The Committee also noted that the manufacturer had provided evidence suggesting that survival was strongly related to transfusion status in patients with MDS. The Committee heard from the clinical specialist that it was unclear whether an increase in transfusion independence would improve overall survival in clinical practice. However, the Committee also noted the comment at consultation that there were data to suggest that patients whose condition responds to therapies that increase haemoglobin concentration may have improved survival compared with untreated patients, and that the Evidence Review Group (ERG), while outlining the uncertainties in the strength of the relationship over time, had accepted this relationship as plausible. Overall the Committee concluded that it was reasonable to assume a relationship between lenalidomide and transfusion independence, and transfusion independence and overall survival, although there remained uncertainty about the exact strength of the relationship and whether the relationship diminished over time.

4.7   The Committee considered the manufacturer's assumption that the risk of progression to acute myeloid leukaemia (AML) was lower in patients whose condition responded to lenalidomide. It noted that the manufacturer had submitted additional information on the rationale for lenalidomide slowing progression to AML, which included literature that showed a relationship between transfusion status and risk of progression to AML (see section 3.42), and also evidence from the pivotal trials, including MDS-004, showing transfusion status was a statistically significant variable for AML progression. The Committee noted, however, that the ERG had highlighted there was also evidence from MDS-004 to show that transfusion status was not a significant variable for progression to AML (see section 3.44). The Committee also noted the safety briefing that had been sent by the manufacturer to healthcare professionals about the use of lenalidomide for MDS, which outlined a 2-year risk of progression to AML of 13.8% in MDS associated with a deletion 5q cytogenetic abnormality. The Committee understood that this was similar to the natural history rate. It was also aware that in studies described in lenalidomide's summary of product characteristics, in people with multiple myeloma, the rate of progression to AML and second primary malignancies was increased. Finally, it heard from the clinical specialist that longer-term data suggest that lenalidomide treatment does not increase the rate of progression to AML. Overall the Committee concluded that there was considerable uncertainty over whether lenalidomide was associated with changes in rates of progression to AML for patients with MDS associated with a deletion 5q cytogenetic abnormality.

4.8   The Committee considered the adverse events associated with lenalidomide treatment from the MDS-004 study. It noted that the most frequently reported adverse events associated with

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lenalidomide treatment were neutropenia and thrombocytopenia. The Committee was also aware that lenalidomide may be associated with higher rates of progression to AML and venous thromboembolism than placebo, although it heard from the clinical specialist that the risk of thromboembolic events did not appear to be problematic and was manageable for patients with low and intermediate-1 risk MDS. It also heard from the clinical specialist and patient experts that adverse events associated with lenalidomide treatment may result in dose reductions but are then generally well tolerated. The Committee concluded that, although lenalidomide is associated with some adverse events, these can be managed by a reduction in dose.

Cost effectiveness

4.9   The Committee considered the manufacturer's economic model and the ERG's critique and exploratory analyses. The Committee discussed overall survival estimates in the manufacturer's model, noting that the manufacturer did not extrapolate survival estimates for the lenalidomide and best supportive care groups from the MDS-004 study because patients in both treatment groups were permitted to cross over after 16 weeks. It noted that, instead, the manufacturer had justified estimating separate survival curves for people who were transfusion dependent or independent by 8 weeks in MDS-004 but not randomised to a treatment arm on the basis that transfusion status was a significant predictor of overall survival in people with MDS. The Committee noted its previous conclusion that this relationship was plausible, although its strength over the 20-year time frame of the model was unclear (see section 4.6). The Committee concluded that, while the strength of the relationship over time was unclear, it was reasonable for the model

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to include a benefit in overall survival for patients whose condition responds to lenalidomide compared with best supportive care.

4.10   The Committee considered the manufacturer's approach to modelling progression to AML. The Committee understood that, because of crossover at 16 weeks in the MDS-004 study, the manufacturer had again estimated separate rates of progression to AML according to transfusion status. This resulted in very small differences in favour of lenalidomide compared with best supportive care in the rate of progression to the AML state. The Committee noted its previous conclusion that it was uncertain if lenalidomide was associated with a change in rates of progression to AML for patients with MDS associated with a deletion 5q cytogenetic abnormality (see section 4.7). Overall the Committee concluded that it was unreasonable for the model to result in any advantage for lenalidomide over best supportive care in the rate of progression to AML, because the relationship was uncertain from the evidence presented.

4.11   The Committee considered the monitoring costs in the model, noting that the manufacturer had assumed that all monitoring would take place at a GP visit. The Committee heard from the clinical specialist that monitoring of people with MDS would be carried out by a haematologist in clinical practice, and that the manufacturer had accepted this modification to the model. The Committee therefore concluded that monitoring would involve the costs of a haematologist visit rather than a GP visit.

4.12   The Committee considered the manufacturer's assumptions about the time to initiation of iron chelation therapy for people who are transfusion dependent. The Committee noted that the manufacturer had made a labelling error in their original model. However, the Committee noted that the manufacturer had explained at

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consultation that the underlying model was correct despite this labelling error. The Committee therefore concluded that no adjustment for iron chelation commencement was needed.

4.13   The Committee considered the utility values associated with transfusion status, noting that these were key drivers of the incremental cost-effectiveness ratio (ICER) estimates in the manufacturer's model. The Committee noted that EQ-5D utility values were collected at the start of the MDS-004 study but not at subsequent follow-up, and that the manufacturer stated it was not possible to reliably estimate utility values by mapping from the FACT-An scores to the EQ-5D because of differences between the EQ-5D utility values collected in the MDS-004 study and those predicted by the mapping exercise. The Committee noted that the manufacturer used values that were taken from a published study (Szende et al. 2009) which estimated utility values according to transfusion dependence and independence directly from people with MDS. It was aware that the utility values from Szende et al. were not in line with the NICE reference case for measuring and valuing health effects, which states that the value of changes in patients' health-related quality of life should be based on public preferences. However, the Committee heard from the patient experts that these health states were a reasonable reflection of the negative impact that transfusion dependence has on health-related quality of life. On balance, the Committee therefore concluded that the utility values used in the manufacturer's model were a reasonable reflection of the impact of transfusion status on health-related quality of life in people with MDS.

4.14   The Committee considered the ICERs resulting from the manufacturer's economic analysis as well as the results of the ERG's exploratory analyses, the manufacturer's additional

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information at consultation, and the ERG's response to the comments. The Committee noted that the manufacturer's base-case ICER for lenalidomide compared with best supportive care was approximately £65,100 per quality-adjusted life year (QALY) gained, which included the cost of routine monitoring performed by a haematologist rather than a GP. It heard from the ERG that applying a half-cycle correction in the manufacturer's model would reduce the manufacturer's ICER to approximately £64,000 per QALY gained, and the probabilistic ICER based on the half-cycle correction would be approximately £67,000 per QALY gained. The Committee also noted that the manufacturer presented an ICER of approximately £68,100 per QALY gained when similar rates of progression to AML for both treatment groups were assumed (see section 3.43). The ERG also stated that applying a half-cycle correction and running the model probabilistically would result in an ICER of approximately £70,000 per QALY gained. The Committee agreed that given the uncertainties in the evidence the most plausible ICER was approximately £70,000 per QALY gained, and concluded that lenalidomide for treating MDS associated with a deletion 5q cytogenetic abnormality could not be recommended as a cost-effective use of NHS resources.

4.15 The Committee discussed how innovative lenalidomide is in its potential to make a significant and substantial impact on health-related benefits. It agreed that the convenience of a new oral treatment and reduction in the need for blood transfusions offered a step change in treatment. The Committee considered that this was already captured in the QALY calculation and that there were no additional gains in health-related quality of life over those already included in the QALY calculations. Therefore, the Committee concluded that the innovative aspects of lenalidomide were already incorporated in the economic analyses.

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4.16   The Committee examined whether there were any potential issues affecting groups protected by equality legislation. The Committee noted comments from some consultees that MDS associated with a cytogenetic abnormality predominately affects older people and women. The Committee also noted the comments from consultees about the Jehovah's Witness group who are unable to receive blood transfusion for religious reasons. 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 lenalidomide 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.

Summary of Appraisal Committee's key conclusions

TAXXX	Appraisal title: Lenalidomide for treating myelodysplastic syndromes associated with a deletion 5q cytogenetic abnormality	Section
Key conclusion		
Lenalidomide is not recommended within its marketing authorisation, that is, for treating transfusion-dependent anaemia caused by low or intermediate-1-risk myelodysplastic syndromes (MDS) associated with a deletion 5q cytogenetic abnormality, when other treatments fail. The Committee agreed that the most plausible incremental cost-effectiveness ratio (ICER) for lenalidomide compared with best supportive care was likely to be greater than £70,000 per quality-adjusted life year (QALY) gained.		1.1, 4.14
Current practice		
Clinical need of patients, including the availability of alternative treatments	The Committee heard from the clinical specialist that the main treatment option currently available for people with MDS associated with a deletion 5q cytogenetic abnormality is best supportive care, which involves regular red blood cell transfusions.	4.1

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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 heard that lenalidomide is an effective targeted therapy with a real impact on the decreased need for blood transfusions. The patient experts agreed that this was a major benefit, with reduced fatigue significantly improving quality of life. The patient experts suggested that lenalidomide is a convenient, effective oral drug that would reduce the need for blood transfusions. The Committee concluded that the convenience of a new oral treatment and the reduction in the need for blood transfusions offered a step-change in treatment.	4.2, 4.15
What is the position of the treatment in the pathway of care for the condition?	Lenalidomide has a marketing authorisation 'for the treatment of patients with transfusion-dependent anaemia due to low- or intermediate-1-risk myelodysplastic syndromes associated with an isolated deletion 5q cytogenetic abnormality when other therapeutic options are insufficient or inadequate'.	2.1
Adverse reactions	The Committee concluded that, although lenalidomide is associated with some adverse events, these can be managed by a reduction in dose.	4.8
Evidence for clinical effectiveness		
Availability, nature and quality of evidence	The Committee concluded that, on the basis of the evidence on transfusion independence and health-related quality of life, lenalidomide is a clinically effective treatment for people with MDS associated with a deletion 5q cytogenetic abnormality. The Committee noted that there was no statistically significant difference in overall survival between the lenalidomide and placebo treatment groups in the MDS-004 study. However the Committee noted the evidence provided by the manufacturer suggesting that survival was strongly related to transfusion status in patients with MDS. The Committee concluded that, although there was uncertainty in the strength of the relationship over time, it was reasonable to assume that lenalidomide improved survival in patients with MDS associated with a deletion 5q cytogenetic abnormality.	4.5, 4.6

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Relevance to general clinical practice in the NHS	The Committee noted that MDS-004 study included a broader range of patients than that specified in the marketing authorisation for lenalidomide, which includes people with transfusion-dependent anaemia due to low- or intermediate-1 risk myelodysplastic syndromes associated with an isolated deletion 5q cytogenetic abnormality when other therapeutic options are insufficient or inadequate. However, the Committee was aware that a significant proportion of the people in the MDS-004 study were covered by the marketing authorisation, and that it would be able to make recommendations on lenalidomide for treating MDS associated with a deletion 5q cytogenetic abnormality on the basis of the whole MDS-0004 study population.	4.4
Uncertainties generated by the evidence	The Committee concluded that there was uncertainty about whether lenalidomide changed rates of progression to acute myeloid leukaemia (AML) in patients with MDS associated with a deletion 5q cytogenetic abnormality.	4.7
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	None was identified.	
Estimate of the size of the clinical effectiveness including strength of supporting evidence	The Committee concluded that, on the basis of the evidence on transfusion independence and health-related quality of life, lenalidomide is a clinically effective treatment for people with MDS associated with a deletion 5q cytogenetic abnormality.	4.5
Evidence for cost effectiveness		
Availability and nature of evidence	The manufacturer developed a de novo Markov-state-transition cost-utility model which simulated cohorts of people with low- to intermediate-1 risk MDS with deletion 5q receiving lenalidomide 10 mg or best supportive care.	3.11
Uncertainties around and plausibility of assumptions and inputs in the economic model	The Committee concluded that, based on the clinical trial data and clinical specialist evidence it was unreasonable for the model to result in any advantage for lenalidomide over best supportive care in the rate of progression to AML.	4.10

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Incorporation of health-related quality-of-life benefits and utility values Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?	The Committee concluded that the utility values used in the manufacturer's model were a reasonable reflection of the impact of transfusion status on health-related quality of life in people with MDS.	4.13
Are there specific groups of people for whom the technology is particularly cost effective?	Not applicable	
What are the key drivers of cost effectiveness?	The Committee noted that the utility values associated with transfusion status were key drivers of the ICER estimates in the manufacturer's model.	4.13
Most likely cost-effectiveness estimate (given as an ICER)	The Committee agreed that the most plausible ICER was likely to be greater than £70,000 per QALY gained.	4.14
Additional factors taken into account		
Patient access schemes (PPRS)	Not applicable	
End-of-life considerations	Not applicable	

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Equalities considerations and social value judgements	The Committee examined whether there were any potential issues affecting groups protected by equality legislation. The Committee noted comments from some consultees that MDS associated with a cytogenetic abnormality predominately affects older people and women. The Committee also noted the comments from consultees about the Jehovah's Witness group who are unable to receive blood transfusion for religious reasons. 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 lenalidomide 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.	4.16

5 Implementation

5.1 NICE has developed tools [link to www.nice.org.uk/guidance/TAXXX] to help organisations put this guidance into practice (listed below). [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.

6 Related NICE guidance

Details are correct at the time of publication. Further information is available on the NICE website.

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- [Azacitidine for the treatment of myelodysplastic syndrome, chronic myelomonocytic leukaemia and acute myeloid leukaemia](#). NICE technology appraisal guidance 218 (2011)

- [Improving outcomes in haemato-oncology cancer](#). NICE clinical guideline CSGHO (2003)

7   Review of guidance

7.1   The guidance on this technology will be considered for review in November 2016 The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Andrew Stevens
Chair, Appraisal Committee
October 2013

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8 Appraisal Committee members and NICE project team

8.1 *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 4 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 Andrew Stevens
Chair of Appraisal Committee C, Professor of Public Health, University of Birmingham

Professor Eugene Milne
Vice Chair of Appraisal Committee C, Deputy Regional Director of Public Health, North East Strategic Health Authority, Newcastle upon Tyne

Professor Kathryn Abel
Director of Centre for Women's Mental Health, University of Manchester

Dr David Black
Medical Director, NHS South Yorkshire and Bassetlaw

Dr Daniele Bryden
Consultant in Intensive Care Medicine and Anaesthesia, Sheffield Teaching Hospitals NHS Trust

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Dr Andrew Burnett
(Formerly) Director for Health Improvement and Medical Director, NHS
Barnet, London

David Chandler
Lay Member

Gail Coster
Advanced Practice Sonographer, Mid Yorkshire Hospitals NHS Trust

Professor Peter Crome
Honorary Professor, Dept of Primary Care and Population Health, University
College London

Dr Maria Dyban
General Practitioner, Kings Road Surgery, Cardiff

Professor Rachel A Elliott
Lord Trent Professor of Medicines and Health, University of Nottingham

Dr Greg Fell
Consultant in Public Health, Bradford Metropolitan Borough Council

Dr Wasim Hanif
Consultant Physician and Honorary Senior Lecturer, University Hospital
Birmingham

Dr Alan Haycox
Reader in Health Economics, University of Liverpool Management School

Dr Peter Jackson
Clinical Pharmacologist, University of Sheffield

Dr Janice Kohler
Senior Lecturer and Consultant in Paediatric Oncology, Southampton
University Hospital Trust

Emily Lam
Lay Member

Dr Allyson Lipp
Principal Lecturer, University of Glamorgan

Dr Claire McKenna
Research Fellow in Health Economics, University of York

Professor Gary McVeigh

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Professor of Cardiovascular Medicine, Queens University Belfast and Consultant Physician, Belfast City Hospital

Dr Grant Maclaine
(Formerly) Director, Health Economics and Outcomes Research, BD, Oxford

Dr Andrea Manca
Health Economist and Senior Research Fellow, University of York

Dr Paul Miller
Director, Payer Evidence, Astrazeneca UK Ltd

Dr Anna O'Neill
Deputy Head of Nursing and Healthcare School/Senior Clinical University Teacher, University of Glasgow

Alan Rigby
Academic Reader, University of Hull

Professor Peter Selby
Consultant Physician, Central Manchester University Hospitals NHS Foundation Trust

Professor Matt Stevenson
Technical Director, School of Health and Related Research, University of Sheffield

Dr Tim Stokes
Senior Clinical Lecturer, University of Birmingham

Dr Paul Tappenden
Reader in Health Economic Modelling, School of Health and Related Research, University of Sheffield

Dr Judith Wardle
Lay Member

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8.2   *NICE project team*

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Helen Tucker/Carl Prescott

Technical Leads

Matthew Dyer

Technical Adviser

Lori Farrar

Project Manager

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9 Sources of evidence considered by the Committee

A. The Evidence Review Group (ERG) report for this appraisal was prepared by Kleijnen Systematic Reviews Ltd:

- Riemsma R, Al M, Blommestein H, Deshpande S, Ryder S, Worthy G, Noake C, Armstrong N, Severens JL, Kleijnen J. Lenalidomide for the treatment of myelodysplastic syndromes associated with deletion 5q cytogenetic abnormality: a Single Technology Appraisal. York: Kleijnen Systematic Reviews Ltd, 2013

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:

- Leukaemia CARE
- MDS UK Patient Support Group
- Rarer Cancers Foundation
- Association of Cancer Physicians
- British Society for Haematology
- Cancer Research UK
- Royal College of Nursing
- Royal College of Pathologists

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- Royal College of Physicians

III. Other consultees:

- Department of Health
- Welsh Assembly Government

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

- Commissioning Support Appraisals Service
- Department of Health, Social Services and Public Safety for Northern Ireland
- Healthcare Improvement Scotland
- National Cancer Research Institute
- Kleijnen Systematic Reviews Ltd
- National Institute for Health Research Health Technology Assessment Programme
- National Collaborating Centre for Cancer

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 lenalidomide for treating myelodysplastic syndromes associated with a deletion 5q cytogenetic abnormality by attending the initial Committee discussion and providing written evidence to the Committee. They were also invited to comment on the ACD.

- Dr David Bowen, Consultant Haematologist, nominated by Royal College of Physicians – clinical specialist
- Fiona Pirilla, Committee Secretary, nominated by MDS UK Patient Support Group – patient expert
- Professor Rodney Taylor, Chairman, nominated by MDS UK Patient Support Group

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

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