

# Lenalidomide for treating myelodysplastic syndromes associated with an isolated deletion 5q cytogenetic abnormality

Technology appraisal guidance

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## Your responsibility

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# 1 Recommendations

- 1.1 Lenalidomide is recommended as an option, within its marketing authorisation, that is for treating transfusion-dependent anaemia caused by low or intermediate-1 risk myelodysplastic syndromes associated with an isolated deletion 5q cytogenetic abnormality when other therapeutic options are insufficient or inadequate. It is recommended only if the company provides it according to the commercial arrangement.

## 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 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. The summary of product characteristics recommends a starting dose of 10 mg orally, once daily, on days 1 to 21 of repeated 28 day cycles, with dose reductions (5.0 mg, 2.5 mg or 2.5 mg every other day) to manage adverse events. Dosage is continued or modified based on clinical and laboratory findings. Lenalidomide is structurally similar to thalidomide, which causes severe birth defects, so a risk minimisation plan has been developed and agreed with the Medicines and Healthcare products Regulatory Agency to avoid fetal exposure to 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 £3,780 and £3,570 respectively (excluding VAT; BNF edition 67). The cost of a 28-day cycle of treatment with 10 mg of lenalidomide (excluding VAT) is £3,780. The pricing arrangement considered during guidance development was that the company (Celgene) had agreed a complex patient access scheme with the Department of Health, in which the NHS paid for lenalidomide treatment for up to 26 monthly cycles. The company subsequently provided free of charge lenalidomide for those people who had more than 26 monthly cycles. A commercial arrangement has now been agreed. This makes lenalidomide available to the NHS with a discount. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations

know details of the discount.

## 3 The company's submission

The Appraisal Committee considered evidence submitted by Celgene and a review of this evidence by the Evidence Review Group (ERG).

### Clinical effectiveness

- 3.1 The company performed a systematic review of the evidence on the clinical effectiveness of lenalidomide for low- or intermediate-1 risk myelodysplastic syndromes (MDS) associated with a deletion 5q cytogenetic abnormality that is red blood cell transfusion dependent. The review identified a single phase 3, randomised, double-blind study (MDS-004), which compared lenalidomide 10 mg (n=69) and lenalidomide 5 mg (n=69) with placebo (n=67). Treatment was given every day of a 28-day cycle, except in the lenalidomide 10 mg arm, in which 10 mg lenalidomide was given on days 1 to 21 only. MDS-004 was a multinational study that enrolled people 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. MDS-004 was stratified according to IPSS karyotype score (0 versus >0; that is, isolated deletion 5q cytogenetic abnormality versus isolated deletion 5q cytogenetic abnormality [76.3%] plus 1 or more additional cytogenetic abnormalities [23.7%]). In the MDS-004 study, 51.8% of the total patient population had had previous erythropoietin therapy (58.5% in the 10 mg lenalidomide treatment arm).
- 3.2 People in MDS-004 who had at least a minor erythroid response (that is, a 50% decrease in transfusion requirements) by week 16 could continue treatment (double-blind) for up to 52 weeks, or until erythroid relapse, disease progression or unacceptable toxicity. People 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. People 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. The company stated that the lenalidomide dose was reduced if dose-limiting toxicities occurred, and complete blood counts were obtained weekly after the development of dose-limiting Grade 3 or 4 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 people (n=205). The safety population included all randomised people who received at least 1 dose of study drug (n=205). The mITT population included people 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 (n=139). Confirmation of deletion 5q status (karyotype analysis) and bone marrow morphology was performed by haematological review after randomisation. Therefore some people not fulfilling the inclusion criteria (that is, people without confirmed deletion 5q status) were included in the ITT population. For the mITT population, 76.3% 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 people 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 adverse events. Health-related quality of life was assessed using the Functional 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 people in the mITT population were transfusion independent for at least 26 weeks 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 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, whichever was earliest) was 30.9 months (range 2.1 to 56.5 months) in the placebo group, 36.1 months (range 0.4 to 57.7 months) in the lenalidomide 10 mg group and 31.8 months (range 0.8 to 59.4 months) in the lenalidomide 5 mg group. Before crossover at 16 weeks, 2 people (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 people (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 to 23.7) at 2 years and 25.1% (95% CI 17.1 to 33.1) at 3 years. Of those who were randomly assigned to placebo and never received lenalidomide (n=11), including 3 people who completed 52 weeks of the study protocol, 4 (36.4%) progressed to AML. Of the people who initially received placebo and then crossed over to lenalidomide 5 mg, 30.4% (17 out of 56) progressed to AML, as did 23.2% (16 out of 69) people in the lenalidomide 5 mg group and 21.7% (15 out of 69) people in the lenalidomide 10 mg group.
- 3.7 The median duration of overall survival follow-up in the safety population was 35.9 months (range 2.1 to 56.5 months) in the placebo group, 36.9 months (range 0.4 to 57.7 months) in the lenalidomide 10 mg group and 35.5 months (range 1.9 to 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), 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 company stated that overall survival was similar between people included in and excluded from the mITT population (p=0.9218). The company 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 International Working Group 2000 criteria. Cytogenetic responses help to establish the degree to which the natural history of myelodysplastic syndromes may be affected by therapy. 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 people treated with lenalidomide 10 mg ( $p = 0.50$  compared with placebo), 31.3% of people treated with lenalidomide 5 mg ( $p = 0.17$  compared with placebo), and 14.3% of people receiving placebo. Similar results were observed in the ITT population. Median time to cytogenetic progression was 93 days (range 85 to 170 days) in the lenalidomide 10 mg group, 85 days (range 83 to 339 days) in the lenalidomide 5 mg group, and 99 days (range 83 to 172 days) in the placebo group.

- 3.9 Health-related quality of life data were collected for 167 people 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 people (lenalidomide 10 mg,  $n = 48$ ; 5 mg,  $n = 45$ ; placebo,  $n = 52$ ). Mean change in FACT-An score from baseline to week 12 was statistically significantly higher in the lenalidomide 10 mg (5.8;  $p < 0.05$ ) and 5 mg (5.9;  $p < 0.05$ ) groups than in the placebo group (-2.5).
- 3.10 The company reported adverse event rates for the double-blind safety population in MDS-004. A higher proportion of people 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 company (1.5% in the placebo group, 1.4% in the lenalidomide 5 mg group and 4.3% in the lenalidomide 10 mg group).

## Cost effectiveness

- 3.11 The company developed a de novo Markov model that simulated cohorts of people 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. A half-cycle correction

was not applied. The time horizon of the model was 20 years based on an average 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%. The company provided 4 models in total, the first being the original base-case (model 1). Model 2 was provided in response to the first appraisal consultation document incorporating revisions to address concerns raised by Committee. Models 3 and 4 were submitted to incorporate the patient access scheme and further revisions to address further concerns raised by the Committee. Sections 3.12 to 3.26 below discuss model 1. Models 2, 3 and 4 are discussed in sections 3.41 to 3.48.

3.12 The model included 13 health states and a death state. The structure was developed to reflect 3 key features of MDS deletion 5q treatment:

- transfusion dependence or independence
- need for iron chelation after a certain number of red blood cell transfusions
- AML progression.

After starting treatment, people move 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, potential hepatic and diabetic complications, and increased risk of cardiac disease caused by red blood cell transfusion. In addition, people who were transfusion dependent or independent with or without complications could develop AML.

3.13 Clinical-effectiveness data from the ITT population in the MDS-004 study were used in the model. The company 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 company assumed that people in the lenalidomide group remained on treatment (10 mg per day for 21 days of a 28-day cycle) 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 blood transfusions for those who were

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

- 3.14 In the model, treatment response was defined as becoming transfusion independent. The proportion of people who became transfusion independent for 56 consecutive days (based on International Working Group 2000 criteria) was 60.9% for the lenalidomide group and 7.5% for the best supportive care group. The response rates for people who received an ESA and a G-CSF in the best supportive care group (21.7%) were taken from a separate study that reported response rates after combination therapy (Jadersten et al. 2005). However, the company 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 company assumed that response rates to monotherapy with either ESA or a G-CSF would be half of those to combination therapy (10.8%).
- 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 of patient crossover in MDS-004, the company used log-rank tests to 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 results showed that the order in which people received treatment in MDS-004 did not have a significant impact on duration of response. Parametric response duration curves were fitted to data from the lenalidomide 10 mg treatment arm in MDS-004 to estimate response duration in the lenalidomide group. The company stated that response duration curves could not be estimated for people in the placebo arm because of insufficient numbers of people whose condition responded to treatment (n=5). Therefore, the company 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 company assumed that people 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 people 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 company also assumed that people who were transfusion dependent had an increased risk of cardiac disease, 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 being transfusion dependent and progressing to cardiac disease.
- 3.17 The company assumed that people who were transfusion dependent started iron chelation therapy to avoid complications associated with iron overload. It was assumed that people started iron chelation therapy when they reached a threshold of 25 red blood cell units. The company also assumed that people had already received 9.15 red blood cell units per 8 weeks based on the average number of units that people 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. People who needed iron chelation moved to either the chelation or chelation failure state. The company assumed that people whose disease responded to treatment continued to receive iron chelation until progression to AML or death. People 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 company stated that survival with MDS is strongly related to transfusion dependence. Data from the MDS-004 study were used to estimate separate mortality curves for people 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 company stated that crossover of people 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 2 trial, MDS-003, and the phase 3 MDS-004 study, resulting in a figure of 3.8 years.

- 3.19 The time to progression to AML in the model was taken from an individual patient-level analysis from the MDS-004 study and was estimated separately for transfusion dependence and independence. 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 people who died from AML was too low. Therefore, the company used data from a study by Wahlin et al. (2001) of older people with AML, including 113 people 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 people remained alive for an unrealistically long time. A Weibull distribution was therefore chosen to estimate the survival time for people who developed AML in the model because it did not result in such a 'long tail'.
- 3.20 The company 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 company 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 people who had neutropenia and thrombocytopenia in the lenalidomide group was adjusted by subtracting those who had these events in the placebo group. The company assumed that any adverse events in the lenalidomide group occurred only in the first 4 cycles of the model. Based on data from MDS-004, the company assumed that only a proportion of people who had neutropenia (27.7%) and thrombocytopenia (6%) needed additional treatment. The company 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 people in the lenalidomide group did not receive treatment. Based on data from the MDS-004 ITT population, it was assumed that 68.7% of people 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, people 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, people 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 company 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. The company presented further analyses on treatment interruptions, which is discussed in sections 3.46 and 3.49.

- 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 company 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 company performed a systematic literature search to identify relevant health-related quality of life data for people with MDS. Four potentially relevant studies were identified (Buckstein et al. 2009 and 2011, Goss et al. 2006 and Szende et al. 2009). The company chose to use Szende et al. (2009). In this study, utility data were collected from 47 people with MDS, of mean age 67 years (including 21 from the UK), using visual analogue scale and time trade-off methods. People were interviewed to elicit utility values for transfusion independence 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 company assumed that people in the AML state had the same utility value as for transfusion dependence (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 people (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 people with low- and intermediate-1 risk MDS from the USA, 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 company.

- 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 Fryback (1993) and Wong (1995). The model did not incorporate utility decrements for people who had neutropenia and thrombocytopenia episodes. The company's justification was that these adverse events were likely to only have a short-term effect on quality of life.
- 3.24 The company's model (model 1) 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 people in the best supportive care group. Drug acquisition prices were obtained from the BNF edition 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 (£1,919.40 per cycle) were taken from [NICE's technology appraisal guidance on azacitidine for the treatment of myelodysplastic syndromes, chronic myelomonocytic leukaemia and acute myeloid leukaemia](#). The costs of thrombocytopenia and neutropenia episodes of £1,636.38 were taken from NHS reference costs 2011 to 2012. 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 company assumed that people had either intravenous desferrioxamine (29%) or oral deferasirox (71%) based on prescription cost analysis data for England (2010), resulting in a total cost of £1,383.39 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 supportive care, monitoring was assumed to occur once every 4 weeks throughout treatment.
- 3.25 The company's model (model 1) estimated 5.69 and 4.53 total undiscounted life



years gained with lenalidomide and best supportive care, respectively. The company'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 estimated an ICER of £58,178 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.

3.26 The company undertook a series of deterministic sensitivity analyses. 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 utility value for the transfusion-dependent state. The company also conducted further scenario analyses, which included altering the population used to estimate the model parameters, altering the proportion in the best supportive care group who received an ESA, altering the number of red blood cell units people 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 company applied alternative utility values for the transfusion-independent (0.91), transfusion-dependent (0.5) and AML (0.5) states taken from the study by Goss et al. (2006), the ICER reduced to £47,621 per QALY gained.

## Evidence Review Group comments

3.27 The ERG considered that the company 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 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 of crossover, only 1 person in the placebo group completed the 52-week double-blind phase. The ERG suggested that one of the main concerns for people receiving lenalidomide is the

incidence of increased clonal evolution and progression to AML. The ERG was concerned that because people could switch from placebo to active drug treatment in MDS-004, the chances of detecting prolonged survival or acceleration of leukaemia progression were limited. Overall, the ERG considered that assessment of the long-term effectiveness of lenalidomide was compromised because people 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, 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 people 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 company's economic model (model 1) was generally well presented and reported. However, the ERG noted that the model described in the company's submission did not fully correspond with the model structure in the electronic model provided. It also noted that the company did not consider progression to intermediate-2 or high-risk MDS in the model because these 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 company'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, because cycle length depends on the changes observed in patient distribution from 1 cycle to another. 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 company's economic model, best supportive care was defined as blood transfusions for transfusion dependence. 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 clinical practice in England.

- 3.31 The ERG considered the response rates used in the company's model, which were based on the MDS-004 ITT population. The ERG noted that the company'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 people 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 people whose condition did not respond immediately to treatment. In response to clarification, the company provided data on the proportion of people 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 of those whose condition responded to treatment were transfusion independent from cycle 1 onwards.
- 3.32 The ERG noted that neither the proportion of people 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 was some uncertainty about the effect of providing ESA to people 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 people (28%) who received ESA and G-CSF therapy. In response to clarification, the company confirmed that these were programming errors. The ERG considered that, in the absence of other available data, it was appropriate for the company 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 company'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 people 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 all people in the model would be monitored by a GP. In response to clarification, the company 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 monitoring in the model. However, the ERG considered that because most people in the model were not treated for adverse events, it would be more reasonable for them 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.

3.35 The ERG noted that the utility values (that is, the measure of health) were taken from a study by Szende et al. (2009). This provided evidence that transfusion independence is associated with significantly better quality of life scores ( $p < 0.001$ ) compared to fewer transfusions and transfusion dependence. The ERG highlighted some concerns with the values applied in the model.

- The Szende study did not conform to the NICE reference case because it was obtained from a sample of people in the UK with MDS rather than a sample of the general UK population without the condition.
- The ERG noted that the model included transfusion dependent and transfusion independent health states. It commented that in clinical practice, people may lie between these states, that is, they are neither completely dependent on transfusion nor completely independent, they need some transfusions. The ERG noted that the transfusion dependent health state included all those that were not transfusion independent, that is, it included those who were completely dependent on transfusion and those who weren't completely dependent, but were not independent either. The ERG commented that the value of 0.65 was elicited for people who were

completely transfusion dependent (requiring a lot of transfusions) and therefore may underestimate the utility value of the transfusion dependent health state, as it also included people who only need a few transfusions.

- The ERG highlighted that the health state description for transfusion dependence in the Szende et al. (2009) study was very broad, in that it covered a range of health problems and the level of transfusion dependence was not the only difference between the health states being compared for the elicitation. This meant that the transfusion-dependent state may have already incorporated some of the adverse events associated with transfusion and chelation therapy, or complications such as cardiac disease, diabetes or hepatic complications. The ERG considered it likely that some double counting was included in the model by also using utility decrements, such as for chelation therapy and complications (see section 3.23).
- The ERG considered that the utility value of 0.65 from the Szende et al. (2009) study for people in the transfusion-dependent state may underestimate utility for the reasons described above. The ERG commented that this would favour lenalidomide because people in the best supportive care group spent a much longer time in this health state compared with the lenalidomide group, thus increasing the QALY difference between lenalidomide and best supportive care in the model.
- The ERG questioned whether it was appropriate to use the same utility values for the AML state as the transfusion-dependent state because this implied that being partly or completely transfusion dependent had the same impact on quality of life as having AML. However, the ERG noted that because there was no difference between the 2 treatment groups in the time spent in the AML state in the model, the impact of the utility value for the AML state was negligible.
- The ERG noted that the company did not apply utility decrements for neutropenia and thrombocytopenia events associated with lenalidomide treatment. The ERG accepted that the impact of these events on health-related quality of life was likely to be small.

3.36 The ERG identified several issues in relation to the resource use and cost estimates used in the company's model. The ERG noted that people 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 people 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 £1,383 to £1,332 per 28-day cycle. The ERG noted that the company's estimated cost of AML treatment of £1,919.40 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 (£1,045) and thrombocytopenia (£1,768) from the NHS reference costs (2011 to 12). The ERG considered that the company'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% of the mean estimate would be more reasonable. Similarly, the ERG noted that the company's probabilistic sensitivity analysis did not account for uncertainty around the number of monitoring visits in both treatment groups.

3.37 The ERG ran the company's model incorporating the following adjustments:

- Programming errors confirmed by the company 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 £1,332 per cycle to include deferiprone.
- Treatment costs of AML were amended to £1,451 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 £1,045 and £1,768 respectively.
- Updated the costs of monitoring, complications and adverse events.

- 3.38 When the ERG included all of these changes in the company's model (model 1) the deterministic ICER without the patient access scheme increased from £56,965 to £62,674 per QALY gained for lenalidomide compared with best supportive care (incremental costs £50,898 and incremental QALYs 0.81). The probabilistic ICER was £65,052 per QALY gained.
- 3.39 The ERG reproduced the company's sensitivity and scenario analyses in the amended model (model 1). 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 company's scenario analyses, the only scenario that had a substantive impact in the ICER was using utility values from Goss et al. (2006), which reduced the ICER to £51,956 per QALY gained (see section 3.26).
- 3.40 The ERG undertook additional scenario analyses. The scenarios that had the most substantial effect on the ICER were the utility value for transition dependence and the proportion of people 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 ICER for lenalidomide compared with best supportive care increased to £68,357 per QALY gained compared with the company's base-case ICER of £56,965 per QALY gained. When the proportion who received intravenous iron chelation therapy was increased from 5.7% to 100%, the ICER reduced to £56,750 per QALY gained. Assuming that people in the transfusion-dependent state would start iron chelation therapy after 4 cycles increased the ICER to £67,428 per QALY gained. Assuming that all monitoring would take place at a haematologist visit increased the ICER to £64,079 per QALY gained.

## Company's response to the appraisal consultation document

- 3.41 The company submitted the results of a systematic literature review to show transfusion dependence was a prognostic factor for overall survival and rate of

progression to AML. Of the 17 studies (mainly retrospective case series or register populations) meeting the inclusion criteria, 16 studies reported statistically significant associations between transfusion status and overall survival. This association was explained by:

- transfusion dependence and anaemia leading to increased death from causes other than leukaemia (particularly cardiac death)
- transfusion dependence and anaemia leading to increased risk of AML and death caused by leukaemia
- transfusion independence after dependency at baseline improving overall survival because of reduced complications from chronic anaemia.

The company 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 people whose condition responded to lenalidomide.

3.42 In response to the appraisal consultation document, the company revised the economic model according to the adjustments described in section 3.37, which increased the base-case ICER from £56,965 to £62,674 per QALY gained (model 2). It also accepted that monitoring would be undertaken by a haematologist rather than a GP, increasing the ICER (model 2) to £65,153 per QALY gained. A model scenario was explored in which the progression to AML was the same for the lenalidomide and best supportive care arms which increased the ICER (model 2) to £68,125 per QALY gained. The company also provided further information to explain a labelling error in its 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 needed. Finally, the company submitted its methods for attempting to map FACT-An scores to EQ-5D and the way it accounted for crossover in the trial arms.

3.43 The ERG considered the additional information submitted by the company, and the updated model (model 2). 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 between transfusion independence and overall survival. However, there was uncertainty in the strength of the relationship between transfusion independence and overall survival 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 in the association between lenalidomide and reduced rate of progression to AML.

## Company's patient access scheme and further revisions to the company's model

3.44 The company has agreed a patient access scheme for lenalidomide with the Department of Health. The company requested permission to submit the patient access scheme as part of the technology appraisal, which was agreed by NICE as an exceptional circumstance. It is a standard scheme, with the NHS paying for up to 26 cycles of treatment with lenalidomide. The company will then provide free-of-charge lenalidomide for people needing treatment beyond 26 cycles, which could take the form of a rebate, vouchers or free stock of the drug. The company provided updated analyses (model 3) that:

- incorporated the patient access scheme – the company assumed that 31.9% would have 26 cycles of treatment and would therefore be eligible for the rebate of free subsequent treatment to the NHS as outlined in the patient access scheme, based on the MDS-004 trial
- included the adjustments stated in section 3.37, including a half-cycle correction
- amended the rate of progression to AML in the lenalidomide arm to be the same as in the best supportive care arm
- assumed routine monitoring by a haematologist rather than a GP.

3.45 The company presented revised analyses (model 3) with and without the patient

access scheme. The resulting deterministic ICERs for lenalidomide compared with best supportive care were £68,125 per QALY gained (without the patient access scheme;) and £24,544 per QALY gained (with the patient access scheme). The mean probabilistic ICER including the patient access scheme was £25,468 per QALY gained. Sensitivity analyses showed that the ICER was most sensitive to median survival from the MDS-003 and MDS-004 trials, with a maximum deterministic ICER of £33,309 per QALY gained. The company presented scenario analyses, including varying utilities, where the ICERs ranged from £19,135 to £25,861 per QALY gained when alternative utility sources were used (Goss and Buckstein, respectively), and varying the selection of survival curves where ICERs ranged from £24,776 to £30,022 per QALY gained.

## Committee request for additional cost-effectiveness analysis

3.46 The Committee were unable to make a decision based on the evidence submitted with the patient access scheme because of uncertainty in the proportion who would receive lenalidomide after 26 cycles, how long they would receive it for, and the impact of dose interruptions. The Committee therefore requested further cost-effectiveness analysis with the patient access scheme to address these uncertainties and better understand how it would apply to clinical practice. The Committee noted that dose interruptions had not appropriately been taken into account when the patient access scheme was incorporated into the model, and that interruptions would delay when the patient access scheme would take effect for people who have dose-interruptions. Cycles may be missed to manage toxicity, which would delay when a patient reached 26 cycles, the point at which the patient access scheme allowed free lenalidomide. The company therefore updated the base case to account for 16 days of treatment interruptions and explored the impact of longer dose interruptions (model 4). The updated base-case ICER was £25,310 per QALY gained for lenalidomide compared with best supportive care. Probabilistic sensitivity analyses estimated a mean ICER of £25,708 per QALY gained. The probability of being cost effective was 25.4% and 64.5% at £20,000 and £30,000 per QALY gained respectively. Increasing the length of interruptions reduced the ICER; accounting for 42 days of treatment interruptions reduced the ICER to £22,209 per QALY gained for lenalidomide

compared with best supportive care.

3.47 At the request of the Committee, the company presented evidence to support the proportion of people who would be expected to be eligible for the patient access scheme (31.9%):

- Published data (Fenaux et al. 2011) from an interim analysis showed that, of those in the 10 mg lenalidomide arm of MDS-004, 38% were still on treatment after 26 cycles. The company applied a correction factor to this value to reduce survival on both arms to the levels seen in real-life practice, subsequently estimating that 31.9% would remain on treatment after 26 cycles in clinical practice.
- Real-world UK data from Celgene's in-house database suggested that 28% of people reached 26 cycles of treatment with lenalidomide.
- Published registry data indicated that response duration ranged from 27.6 to 36 months.

The company presented a threshold analysis that showed if the proportion eligible for the patient access scheme was less than 27%, the ICER (model 4) would be greater than £30,000 per QALY gained.

3.48 The patient access scheme presented by the company would not take effect until after a minimum of 2 years, or longer with dose interruptions. At the request of the Committee, the company presented further cost-effectiveness analyses, including scenarios for various time horizons to understand how the cost effectiveness would change over time as the patient access scheme was implemented. Applying time horizons of 2, 3, 5 and 10 years in model 4 gave ICERs of £119,876, £63,780, £30,923 and £23,420 per QALY gained respectively for lenalidomide compared with best supportive care.

3.49 The ERG validated the changes to the company's model, confirming that the patient access scheme was incorporated appropriately. It agreed with the company that the real-world evidence suggested that about 30% of people reach 26 cycles of treatment, and the ERG stated that this was a reasonable assumption. It commented that the company's estimate of 16 days of treatment interruptions may be an underestimate and it could be closer to 19 days. The ERG

showed that this had a negligible impact on the ICER with the company's base case increasing from £25,310 per QALY gained to £25,455 per QALY gained. It stated that the first 5 years of the model were more certain than the later years because they were based on available data. The ERG noted that most of the QALY gains in the model were in these first 5 years (64%), and that 90% of the QALY gains occur within 10 years.

3.50 Full details of all the evidence are in the [committee papers](#).

## 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 low- or intermediate-1 risk myelodysplastic syndromes (MDS) associated with a deletion 5q cytogenetic abnormality when other therapeutic options are insufficient or inadequate, 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 an isolated 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 an isolated deletion 5q cytogenetic abnormality when other therapeutic options are insufficient or inadequate). It heard from the clinical specialist that the main treatment option currently available for people with low- or intermediate-1-risk MDS associated with an isolated 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 people. The clinical specialist also stated that some people 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. Therefore, the Committee agreed that as defined in the scope, best supportive care was the appropriate comparator
- 4.2 The Committee heard from the clinical specialist that lenalidomide is an effective targeted therapy which reduces 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 having 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 condition. The patient experts suggested that lenalidomide, by contrast, is a convenient, effective oral drug that reduces the need for blood transfusions. The Committee recognised the need for treatments that would reduce blood transfusion dependence for people with MDS associated with an

isolated deletion 5q cytogenetic abnormality.

## Clinical effectiveness

- 4.3 The Committee discussed the clinical effectiveness of lenalidomide in people with low- or intermediate-1 risk MDS associated with an isolated deletion 5q cytogenetic abnormality when other therapeutic options are insufficient or inadequate. It noted that the evidence presented by the company was taken primarily from the MDS-004 study. This included a broader range of people than that specified in the marketing authorisation and NICE scope for lenalidomide, because the marketing authorisation stated 'when other therapeutic options are insufficient or inadequate', which was not an inclusion criteria for the study, and therefore those on the trial may have a better prognosis than the population specified by the marketing authorisation. In addition, the study included people with low- or intermediate-1 risk MDS associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities, whilst the marketing authorisation specified an isolated deletion 5q cytogenetic abnormality. The Committee heard from the company during consultation that the additional cytogenetic abnormalities included in the trial population may mean the trial population had a poorer prognosis than that of the population covered by the marketing authorisation. The Committee agreed that, on balance, the study was generalisable to the marketing authorisation population, and how lenalidomide would be used in clinical practice. 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 an isolated deletion 5q cytogenetic abnormality.
- 4.4 The Committee considered the results of the MDS-004 study. It noted that the rates of transfusion independence (at 26 weeks, lenalidomide 10 mg: 56.1%, placebo: 5.9%;  $p < 0.001$ , see section 3.5) and improvements in the Functional Assessment of Cancer Therapy-Anaemia (FACT-An) questionnaire (mean change, lenalidomide 10 mg: 5.8, placebo: -2.5;  $p < 0.05$ . See section 3.9) were significantly better in people treated with lenalidomide compared with placebo. The Committee concluded that lenalidomide is a clinically effective treatment for people with low- or intermediate-1-risk MDS associated with an isolated deletion 5q cytogenetic abnormality when other therapeutic options are insufficient or

inadequate.

4.5 The Committee discussed overall survival from MDS-004, noting that overall survival with placebo and lenalidomide was greater than 35 months and that there was no statistically significant difference between lenalidomide and placebo (lenalidomide 10 mg: 36.9 months, placebo: 35.9 months). It was aware that people in the placebo arm could cross over to lenalidomide treatment after 16 weeks (see section 3.2), and therefore the overall survival benefit of lenalidomide compared with placebo may be under estimated. The Committee noted that the company had presented separate mortality curves for people who were transfusion dependent or independent at 8 weeks in MDS-004 which suggested that survival was strongly related to transfusion status in people with low or intermediate-1 risk MDS associated with a deletion 5q cytogenetic abnormality. The Committee noted that the company's comments in response to consultation included an updated analysis of these data at 7 years, which continued to support a link between transfusion independence and overall survival. The Committee also considered the following:

- ERG comments that it was reasonable to assume a two-step relationship between lenalidomide response and transfusion independence, and then between transfusion independence and overall survival (see section 3.43).
- A consultation comment from a professional group that data suggested people with low risk MDS and anaemia, whose condition responds to therapies that increase haemoglobin concentration, have improved survival compared with those who did not receive treatment.
- The ERG clinical expert had advised that there were uncertainties in the strength of the relationship between transfusion dependence and overall survival.
- A clinical specialist stated that it was unclear if an increase in transfusion independence would improve overall survival in clinical practice, in the population specified by the marketing authorisation.

Overall the Committee concluded that it was plausible for lenalidomide to indirectly improve overall survival by improving transfusion independence.

4.6 The Committee discussed progression to acute myeloid leukaemia (AML). It

understood from the company's systematic review that published data showed higher transfusion independence rates were associated with reduced risk of progression to AML (see section 3.41). The Committee noted that the company had stated transfusion status was a statistically significant predictor for AML progression in MDS-004, but that the ERG had presented contradictory evidence (see section 3.43). The Committee was aware of the lenalidomide safety briefing sent from the company to healthcare professionals that outlined a 13.8% 2-year risk of AML progression with lenalidomide treatment for MDS associated with a deletion 5q cytogenetic abnormality, and that lenalidomide's summary of product characteristics stated lenalidomide was associated with an increase in AML progression and second primary malignancies in people with multiple myeloma. However, it heard from the clinical specialist that longer-term data suggest that lenalidomide treatment does not increase the rate of AML progression in people who have low or intermediate-1 risk MDS with deletion 5q cytogenetic abnormality. The Committee concluded that there was considerable uncertainty over whether lenalidomide was associated with changes in the rates of AML progression for people with low or intermediate-1 risk MDS associated with an isolated deletion 5q cytogenetic abnormality when other therapeutic options are insufficient or inadequate.

- 4.7 The Committee considered adverse reactions associated with lenalidomide treatment from the MDS-004 study. It noted that the most frequently reported adverse reactions associated with lenalidomide treatment were neutropenia and thrombocytopenia. The Committee was also aware that lenalidomide may be associated with higher rates of venous thromboembolism than placebo. However, it heard from the clinical specialist that the risk of thromboembolic events was manageable for people with low- and intermediate-1 risk MDS. It heard from the clinical specialist and patient experts that adverse reactions associated with lenalidomide treatment are managed with dose interruptions and are generally well tolerated. The Committee concluded that, although lenalidomide is associated with some adverse reactions, these can be managed by dose interruptions.

## Cost effectiveness

- 4.8 The Committee considered the company's original economic model, the



company's revised economic model, the company's revised economic model with the patient access scheme, and the ERG's critique and exploratory analyses. It acknowledged that the company had amended the model in response to earlier concerns that were raised by the ERG and the Committee (sections 3.37 and 3.44). These amendments included the:

- costs associated with iron chelation, AML and thrombocytopenia
- incorporation of the patient access scheme
- rate of AML progression which was assumed to be the same for lenalidomide and best supportive care
- monitoring being conducted by a haematologist (rather than GP).

The Committee concluded that the updated models were appropriate for decision-making.

4.9 The Committee discussed further the overall survival estimates as presented in the company's models, and considered the following:

- The company did not extrapolate survival estimates for the lenalidomide and best supportive care arms from the MDS-004 study because people could cross over after 16 weeks.
- The company had estimated survival based on transfusion dependency at 8 weeks in MDS-004, stating that transfusion status was a predictor of overall survival in people with MDS (see section 4.5).

The Committee agreed that increased transfusion independence could be associated with improved survival but recognised that its strength over the 20-year time frame of the model was unclear (see section 4.6). The Committee concluded that, although the strength of the relationship was uncertain, it was reasonable for the model to include some benefit in overall survival for people whose condition responds to lenalidomide compared with best supportive care.

4.10 The Committee considered the utility values associated with transfusion status. 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 company 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 mapping. The Committee noted that the company used values that were taken from a published study (Szende et al. 2009) that derived utility values according to transfusion dependence and independence directly from people with MDS. It considered the ERG's comments that using a utility value of 0.65 for people in the transfusion-dependent state may favour lenalidomide because people in the best supportive care group spent a much longer time in this health state. This would increase the QALY difference between the treatment arms. 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 health-related quality of life should be based on public preferences rather than people who have the condition. However, the Committee heard from the patient experts that the utility values used in the company's base-case analyses were a reasonable reflection of the negative impact that transfusion dependence has on health-related quality of life. It noted that sensitivity analyses which varied the utility values in model 4, including the patient access scheme, gave a range of ICERs between £19,700 and £26,700 per QALY gained (base case: £25,300 per QALY gained) for lenalidomide compared with best supportive care. The Committee concluded that the utility values were a reasonable reflection of the impact of transfusion status on health-related quality of life in people with low or intermediate-1 risk MDS associated with deletion 5q cytogenetic abnormality, and could therefore be used for decision-making in this appraisal.

- 4.11 The Committee discussed the patient access scheme, noting that it was not a simple discount. The NHS pays for lenalidomide treatment for the first 26 cycles, after which it is provided free of charge, and therefore the whole population would not benefit from the reduction in price because only some people, those receiving it after 26 cycles, would be eligible. The Committee noted that the reduction in costs achieved through the patient access scheme would be based on the number of people remaining on treatment after 26 cycles, and how long they survived and continued treatment. The Committee was aware that the data supporting survival after 26 cycles were from small numbers in the MDS-004 trial (less than 38 people), and were therefore very uncertain. The Committee discussed whether the assumption in the model that 31.9% of people would

remain on treatment for more than 26 cycles was realistic, and whether the cost savings associated with the patient access scheme were likely to be realised in clinical practice. The Committee considered the company's evidence that supported the assumption of 31.9% of people reaching 26 cycles in practice (see section 3.47), and noted that this was supported by a clinical specialist. It was concerned, however, about discrepancies between this estimate and those implied by the published paper, but heard from the company that this was because the published paper included data from an earlier time point. The Committee agreed that, because the proportion of people surviving beyond 26 cycles in clinical practice was uncertain (see above and section 4.5), so were the potential cost savings from the patient access scheme, and therefore further validation of the proportion of people on treatment beyond 26 cycles was still required. The Committee recognised that the probabilistic sensitivity analysis presented by the company was unlikely to have captured the uncertainty of the patient access scheme in terms of the proportion who would survive beyond 26 cycles. It noted that the base case of model 4 (see sections 3.46 to 3.49) was associated with a 25% chance of lenalidomide being cost effective at £20,000 per quality-adjusted life year (QALY) gained (and 65% at £30,000 per QALY gained). It also noted that, if the proportion of people who reached 26 cycles was less than 27%, the ICER would be greater than £30,000 per QALY gained. The Committee agreed that the ICER was uncertain but accepted that a commitment from the company to publish data on the proportion of people on treatment beyond 26 cycles would provide reassurance that the patient access scheme will provide value to the NHS.

- 4.12 The Committee noted that as the patient access scheme was based on the number of treatment cycles, any treatment interruptions would delay when the patient access scheme would take effect and therefore delay the time to the NHS receiving the rebate or discount. The Committee acknowledged that accounting for treatment interruptions reduced the ICER minimally (from £25,300 with 16 days of interruptions to £22,200 with 42 days; see section 3.46). The Committee was aware that accounting for treatment interruptions in the model reduced lenalidomide costs but did not affect treatment benefit. The Committee was aware that the nature of the patient access scheme meant that accounting for treatment interruptions introduces uncertainty about when people would reach 26 cycles of treatment, and therefore when the savings from the patient access scheme could be claimed by the NHS. It heard from the company that

they actively monitor the number of cycles that people receive and that this should provide reassurance that the scheme would be realised in practice. The Committee concluded that although treatment interruptions introduce uncertainty on the timing of when the patient access scheme could be claimed, this did not have a substantial impact on the ICER.

4.13 The Committee considered the ICERs resulting from the company's economic analyses, as well as the results of the ERG's exploratory analyses. The Committee noted that the revised company's base-case ICER, which included the patient access scheme and accounted for treatment interruptions (model 4; see sections 3.46 to 3.49), for lenalidomide compared with best supportive care was approximately £25,300 per QALY gained. The Committee agreed that the patient access scheme increased all of the uncertainties, and there was a risk that savings from the patient access scheme would not be realised in clinical practice. The Committee acknowledged that the data collection committed to by the company will ensure that the uncertainties of the assumptions used to model the patient access scheme can be addressed when the guidance is reviewed. However, it would not be able to address the loss in health benefits for other patients in the NHS that may result in the interim from lenalidomide not being a cost effective use of NHS resources. It understood that the company is keen to work with the Department of Health should such a situation arise, to ensure that the NHS realises the full financial benefits of the patient access scheme. The Committee concluded that lenalidomide for treating MDS associated with an isolated deletion 5q cytogenetic abnormality was a cost-effective use of NHS resources, when taking these assurances into account.

4.14 The Committee discussed how innovative lenalidomide is in its potential to make a significant and substantial impact on health-related benefits. It heard about the notable benefits of lenalidomide from patient and professional groups during consultation. It agreed that the convenience of a new oral treatment and reduction in the need for blood transfusions meant that lenalidomide offered a substantial step change in treatment.

4.15 The Committee examined whether there were any potential issues affecting groups protected by equality legislation. The Committee 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 people, or about the effectiveness of lenalidomide in this population. Therefore the Committee agreed that it did not need to amend any of its recommendations for the group of people unable to receive blood transfusions.

## 5 Implementation

- 5.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 3 months of its date of publication.
- 5.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document.
- 5.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has transfusion-dependent anaemia caused by low or intermediate-1-risk myelodysplastic syndromes (MDS) associated with an isolated deletion 5q cytogenetic abnormality and the healthcare professional responsible for their care thinks that lenalidomide is the right treatment, it should be available for use, in line with NICE's recommendations.

## 6 Recommendations for further research

6.1 The Committee noted that the cost effectiveness of lenalidomide compared with standard care for people with low- or intermediate-1-risk MDS associated with an isolated deletion 5q cytogenetic abnormality when other therapeutic options are insufficient or inadequate, was sensitive to whether the patient access scheme would be realised in clinical practice. The Committee agreed that it would be critical to generate evidence to support the following:

- The proportion of people who become eligible for the patient access scheme, that is, that they remain on treatment beyond 26 cycles.
- The benefit of lenalidomide after 26 cycles, that is the associated overall survival and health related quality of life for those who remain on treatment beyond 26 cycles.

# 7 Appraisal Committee members, guideline representatives and NICE project team

## 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



**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

**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 Janice Kohler**

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

**Emily Lam**

Lay Member

**Dr Nigel Langford**

Consultant in Clinical Pharmacology and Therapeutics and Acute Physician Leicester Royal Infirmary

**Dr Allyson Lipp**

Principal Lecturer, University of South Wales

**Dr Claire McKenna**

Research Fellow in Health Economics, University of York

**Professor Gary McVeigh**

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 Suzanne Martin**

Reader in Health Sciences

**Professor Stephen O'Brien**

Professor of Haematology, Newcastle University

**Dr Anna O'Neill**

Deputy Head of Nursing and Healthcare School and Senior Clinical University Teacher, University of Glasgow

**Dr Malcolm Oswald**

Lay member

**Alan Rigby**

Academic Reader, University of Hull

**Professor Peter Selby**

Consultant Physician, Central Manchester University Hospitals NHS Foundation Trust

**Cliff Snelling**

Lay member

**Professor Iain Squire**

Consultant Physician, University Hospitals of Leicester

**Professor Matt Stevenson**

Technical Director, School of Health and Related Research, University of Sheffield

**Dr Paul Tappenden**

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

**Professor Robert Walton**

Clinical Professor of Primary Medical Care, Barts and The London School of Medicine & Dentistry

**Dr Judith Wardle**

Lay Member

**Dr Paul Miller**

Director, Payer Evidence, AstraZeneca UK Ltd

## **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.

**Christian Griffiths, Carl Prescott, Helen Tucker**

Technical Leads

**Melinda Goodall**

Technical Adviser

**Nicole Fisher**

Project Manager

## 8 Sources of evidence considered by the Committee

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

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). Companies or sponsors were also invited to make written submissions. Professional or specialist and patient or carer groups, and other consultees, had the opportunity to give their expert views. Companies or sponsors, professional or specialist and patient or carer groups, and other consultees, also have the opportunity to appeal against the final appraisal determination.

Company or sponsor:

- Celgene UK

Professional or specialist and patient or carer groups:

- Royal College of Nursing
- Royal College of Physicians
- Royal College of Pathologists
- The British Society for Haematology
- MDS UK Support Group
- Rarer Cancer Foundation
- Leukaemia Care

Other consultees:

- None

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

- National Collaborating Centre for Cancer

The following individuals were selected from clinical specialist and patient expert nominations from the non-company or 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.

- None

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

- Celgene

# Update information

**June 2019:** Sections 1 and 2 updated to include a new commercial arrangement.

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