NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Premeeting briefing

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

This premeeting briefing is a summary of:

- the evidence and views submitted by the manufacturer, the consultees and their nominated clinical specialists and patient experts and
- the Evidence Review Group (ERG) report.

It highlights key issues for discussion at the first Appraisal Committee meeting and should be read with the full supporting documents for this appraisal.

Please note that this document is a summary of the information available before the manufacturer has checked the ERG report for factual inaccuracies.

Key issues for consideration

- The population in the manufacturer's submission includes people with transfusion-dependent anaemia due to low- or intermediate-1 risk myelodysplastic syndromes associated with a deletion 5q cytogenetic abnormality (1 or more cytogenetic abnormalities). This population reflects the patient population included in the MDS-004 trial, which forms the basis of the manufacturer's submission. However, the European Medicines Agency has announced a positive opinion for a more restricted population, 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. This group constitutes 76.3% of the total patient population in the MDS-004 study. Does the Committee consider the evidence provided by the manufacturer to be relevant and sufficient for

NICE to issue guidance on lenalidomide for treating myelodysplastic syndromes associated with a deletion 5q cytogenetic abnormality?

Clinical effectiveness

- Data were reported for two populations in the MDS-004 study: the intention-to-treat (ITT) population which included all randomised patients and the modified ITT (mITT) population, which included patients with centrally confirmed low- or intermediate-1-risk MDS with del(5q) and documented RBC transfusion-dependence, who received ≥1 dose of study drug. Does the Committee consider that differences between these two populations could influence the clinical effectiveness estimates which were based on the mITT population and the cost effectiveness estimates which were based on the ITT population?
- The clinical effectiveness data in the manufacturer's submission were taken from a single trial (MDS-004), in which patients were allowed to switch treatment at 16 weeks. What is the Committee's view on the likely long-term impact of this on overall survival and progression to acute myeloid leukaemia for lenalidomide compared with placebo?
- Does the Committee consider that the manufacturer should have formally adjusted for crossover in MDS-004 using statistical method in order to obtain reliable estimates of overall survival?

Cost effectiveness

- The manufacturer assumed that 28% of people receiving best supportive care would be given an ESA for 3 cycles and that people who did not respond to an ESA as part of best supportive care would receive a G-CSF for 3 cycles. Does the Committee accept that best supportive care as represented in the cost effectiveness analysis is similar enough to patient experience in UK clinical practice?

- Does the Committee consider that utility estimates in the manufactures model should have been derived by mapping FACT-An scores collected in the MDS-004 trial to EQ-5D utility values?
- The sensitivity analyses conducted by both the manufacturer and the ERG showed that the cost-effectiveness of lenalidomide compared with best supportive care was sensitive to the utility values associated with transfusion dependence and independence. What is the Committee's view on the validity of the utility values used in the cost-effectiveness analysis?
- Does the Committee accept the ERGs view that the description of the health states used to estimate the utility values associated with transfusion dependence and independence in the model, may have been too broad and, as a result, over estimated the impact of transfusion dependence on health-related quality of life in the model when combined with utility decrements associated with adverse events?
- The manufacturer's sensitivity analyses also showed that the cost-effectiveness estimates were fairly sensitive to the proportion of people who had a second treatment interruption with lenalidomide. Does the Committee consider that it was acceptable for the manufacturer to assume that treatment interruptions would only affect the costs and not the clinical effectiveness of lenalidomide treatment?
- Does the Committee agree with the ERG's alternative approaches to estimating the costs of (i) iron chelation therapy; (ii) acute myeloid leukaemia treatment and; (iii) neutropenia and thrombocytopenia episodes?
- The manufacturer's model used data on the proportion of patients who were transfusion dependent or independent at 8 weeks in MDS-004 to estimate overall survival in both treatment groups. Does the Committee consider this to be a reasonable approach?
- Taking into account the exploratory analyses and corrections made by the ERG, what does the Committee consider to be the most plausible

incremental cost-effectiveness ratio (ICER) for lenalidomide compared with best supportive care?

- The manufacturer considers lenalidomide to be an innovative treatment for myelodysplastic syndromes associated with a deletion 5q cytogenetic abnormality. Does the Committee agree?

1 Background: clinical need and practice

1.1 The myelodysplastic syndromes (MDS) are a diverse group of haematological disorders in which the bone marrow functions abnormally and insufficient numbers of mature blood cells are produced. Red blood cells, white blood cells and platelets may all be affected by MDS, resulting in life threatening disease, with anaemia and increased risk of bleeding and infections. MDS affect patients' quality of life because of debilitating symptoms such as fatigue and dyspnoea, treatment regimens involving hospitalisation with intravenous drug infusions and blood transfusions, and complications such as severe infections.

1.2 MDS are graded using the International Prognostic Scoring System (IPSS), and the French-American-British (FAB) and World Health Organisation (WHO) classification systems. Based on the proportion of leukaemic cells (or 'blasts'), bone marrow cytogenetic findings, and the presence of blood cytopenia, the IPSS classifies outcome as low-risk, intermediate-1 risk, intermediate-2 risk or high-risk. Low or intermediate-1 risk MDS together form approximately 70% of all MDS.

1.3 The annual incidence of MDS is estimated at 4 per 100,000, but incidence increases with age and is 30 per 100,000 per year in people over 70 years of age. Many cases remain undiagnosed. There were 1993 people newly diagnosed with MDS in England in 2004, with over 90% of patients aged over 60 at the time of

diagnosis. Deletion of chromosome 5q is one of the most common cytogenetic abnormalities in MDS, occurring in 16% to 28% of patients. Median survival with low risk and intermediate-1 risk MDS is 5.7 years and 3.5 years respectively. It can be less than 6 months for people with high risk MDS.

1.4 The mainstay of treatment for MDS is best supportive care which includes blood transfusions to control the symptoms of bone marrow failure and antibiotics to treat or prevent infection. Low-dose standard chemotherapy or immunosuppressive therapies are used for some patients. For people with low risk MDS, often a preferred approach is one of no active treatment or 'watchful waiting' and for some people, stem cell transplantation is a potentially curative treatment option. Many patients become red blood cell transfusion dependent, particularly those with low or intermediate-1 risk MDS. A major goal of treatment is then to achieve transfusion independence and a number of treatments can be used to reduce or eliminate the transfusion need for MDS patients. Although growth factors such as granulocyte colony-stimulating factor (G-CSF) and erythropoietin (EPO) can sometimes be used successfully in the early stages of MDS, over time, patients can become unresponsive and increasingly dependent on blood transfusions.

2 The technology

2.1 Lenalidomide (Revlimid, Celgene) is a structural analogue of thalidomide. Its mechanism of action includes anti-neoplastic, anti-angiogenic, pro-erythropoeitic, and immunomodulatory properties. Lenalidomide inhibits proliferation of certain haematopoietic tumour cells, enhances T cell- and Natural Killer (NK) cell-mediated immunity, increases foetal haemoglobin production by CD34+

haematopoietic stem cells and inhibits production of pro-inflammatory cytokines.

2.2 Lenalidomide does not currently have UK marketing authorisation for the treatment of MDS. The Committee for Medicinal Products for Human Use has announced a positive opinion for lenalidomide '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'. The recommended starting dose of lenalidomide for adults over 18 years is 10 mg orally once daily on days 1 to 21 of repeated 28-day cycles. Treatment with lenalidomide is continued until erythroid relapse, disease progression or unacceptable adverse effects occur. For full details, see the summary of product characteristics.

2.3 Lenalidomide must be initiated and monitored under the supervision of physicians experienced in the management of MDS (that is, hospital specialists). It is recommended that all patients see their GP before treatment, every week for the first eight weeks and then monthly thereafter. At each of these visits a full blood count test will be carried out to monitor for cytopenias. Women of childbearing potential require pregnancy testing every four weeks as part of the Pregnancy Prevention Programme, since lenalidomide is expected to have teratogenic effects if taken during pregnancy.

2.4 The summary of product characteristics lists the following adverse reactions for lenalidomide: fatigue, neutropenia, constipation, diarrhoea, muscle cramp, anaemia, thrombocytopenia, and rash. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.5 Lenalidomide is available in 21 day packs of 10 mg and 5mg capsules at net prices of £3780 and £3570 respectively (excluding VAT; 'British national formulary' [BNF] edition 64). The manufacturer estimated the cost of a 28-day cycle of treatment with 10mg of lenalidomide (excluding VAT) to be £3780. Costs may vary in different settings because of negotiated procurement discounts.

3 Remit and decision problem(s)

3.1 The remit from the Department of Health for this appraisal was: To appraise the clinical and cost effectiveness of lenalidomide within its licensed indication for the treatment of myelodysplastic syndromes associated with a deletion 5q cytogenetic abnormality in people with red blood cell transfusion dependence.

	Final scope issued by NICE	**Decision problem addressed in the submission**
Population	Adults with myelodysplastic syndromes (MDS) associated with a deletion 5q cytogenetic abnormality and who are red blood cell transfusion dependent	Same as in the final scope

The ERG noted that the population identified in the final scope included people with intermediate-2 and high risk MDS, whereas the manufacturer had only sought a marketing authorisation for patients with transfusion-dependent due to low- or intermediate-1 risk MDS associated with a deletion 5q cytogenetic abnormality.

	Final scope issued by NICE	**Decision problem addressed in the submission**
Intervention	**Lenalidomide**	**Same as in final scope**

Comparators	For people with intermediate-1 or low risk MDS: • Best supportive care including blood transfusions For people with intermediate-2 and high risk MDS: • Azacitadine • Stem cell transplantation	For people with intermediate-1 or low risk MDS: • Best supportive care including blood transfusions

The manufacturer did not include azacitadine or stem cell transplantation as comparators because the population in its submission did not include patients with intermediate-2 and high risk MDS.

	Final scope issued by NICE	**Decision problem addressed in the submission**
Outcomes	• overall survival • progression-free survival (including time to transformation to AML or death) • response rates, including haematologic response and improvement • frequency of blood-transfusions (including blood-transfusion independence) • serious infections • adverse effects of treatment • health-related quality of life.	Same as in final scope

The ERG noted that the outcome 'frequency of blood transfusions (including blood-transfusion independence)' was not reported in the manufacturer's submission. The ERG also noted that serious infections were reported for grade 3 or 4 pneumonia only, and health-related quality of life was measured in the trial using Functional Assessment of Cancer Therapy-Anaemia (FACT-An) scores.

	Final scope issued by NICE	Decision problem addressed in the submission
Economic evaluation	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. The availability of any patient access schemes for comparators should be taken into account in the economic analysis. Costs will be considered from an NHS and Personal Social Services perspective.	Same as in final scope

4 Clinical-effectiveness evidence

4.1 The manufacturer performed a systematic review of the evidence on the clinical effectiveness of lenalidomide and comparator therapies for patients with low- or intermediate-1 risk MDS associated with del(q) cytogenetic abnormality who are red blood cell (RBC) transfusion dependent. The review identified one phase III, randomised, double-blind, placebo-controlled trial (MDS-004) that 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 of adults with MDS who were transfusion-dependent with International Prognostic Scoring

System (IPSS) low risk (49%) or Intermediate-1 risk (51%) MDS with deletion 5q cytogenetic abnormality (del (5q)). Patients were stratified according to IPSS karyotype score (0 versus >0; that is, isolated del(5q) abnormality versus del (5q) plus one or more additional cytogenetic abnormalities). In the MDS-004 study, patients with 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 without a minor erythroid response by week 16 were permitted to 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.

4.2 3 study populations were defined in MDS-004: the intention-to-treat (ITT), the safety population (n=205) and modified-ITT (mITT) population. The ITT population included all randomised patients (n=205). The safety population included all randomised patients who received ≥1 dose of study drug (n=205). The mITT population included patients with centrally confirmed low- or intermediate-1-risk MDS with del(5q) and documented RBC transfusion-dependence, who received ≥1 dose of study drug. Confirmation of del(5q) status (karyotype analysis) and bone marrow morphology was performed by central haematological review after randomisation, therefore patients not fulfilling the inclusion criteria were included in the ITT population. For the mITT population, 76.3% of patients had an isolated del(5q) cytogenetic abnormality

and 23.7% had del(5q) plus one or more additional cytogenetic abnormalities. The baseline characteristics of the patients in the treatment arms for the mITT population were similar (for further details, see table 7 page 47 of the manufacturer's submission).

4.3 The primary endpoint of the MDS-004 trial was transfusion independence lasting ≥26 consecutive weeks. Secondary endpoints 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, acute myeloid leukaemia (AML) progression and safety. Health-related quality of life was assessed using the FACT-An questionnaire at Weeks 12, 24, 36 and 48.

4.4 The manufacturer stated that the dose of lenalidomide or placebo was reduced if dose-limiting toxicities occurred, and complete blood counts were to be obtained weekly following the development of dose-limiting neutropenia or thrombocytopenia. Lenalidomide dosing was reduced as follows: lenalidomide 5 mg (starting dose), dose level −1 (5 mg every other day), dose level −2 (5 mg twice-weekly), and dose level −3 (5 mg weekly); lenalidomide 10 mg (starting dose), dose level −1 (5 mg daily), dose level −2 (5 mg every other day), and dose level −3 (5 mg twice-weekly); patients not tolerating dose level −3 discontinued treatment. For Grade 4 neutropenia and thrombocytopenia episodes, lenalidomide treatment was also interrupted and resumed at a decreased dose level.

4.5 For the double-blind phase of MDS-004, statistically significantly more patients in the mITT population achieved the primary endpoint of RBC transfusion independence for ≥26 weeks with lenalidomide 10 mg (56.1%) and 5 mg (42.6%) than with placebo

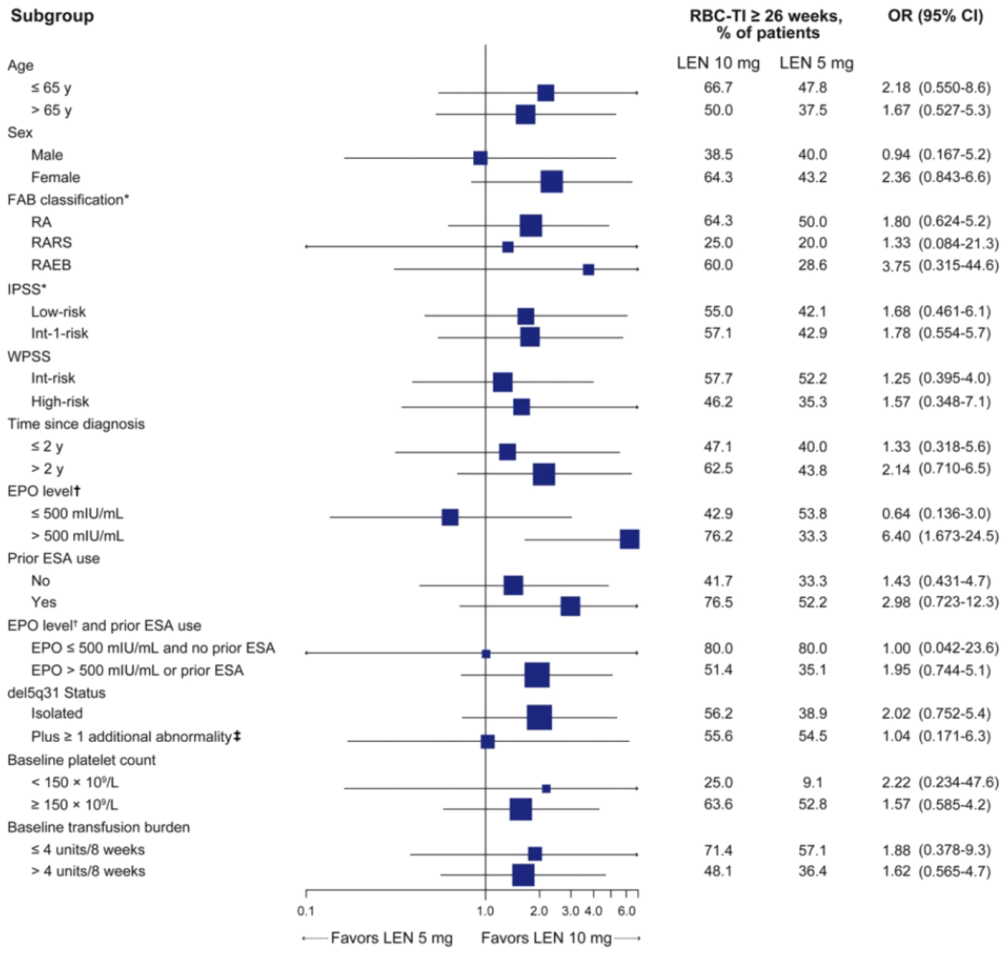
(5.9%; p<0.001 versus both lenalidomide groups). Using the International Working Group (IWG) 2000 and 2006 criteria for erythroid response, RBC transfusion independence rates for ≥ 8 weeks in the mITT population were also statistically significantly higher for the lenalidomide 5 mg and 10 mg treatment groups compared to placebo. Similar results were obtained for the ITT population. Median duration of RBC transfusion independence for ≥ 8 weeks was not reached in the lenalidomide 5 mg or 10 mg treatment groups after a median follow-up of 1.55 years. A summary of the results for the primary endpoint of RBC transfusion independence is presented in table 1.

Table 1. Erythroid response, as assessed by RBC transfusion independence for ≥26 weeks or ≥8 weeks (double-blind phase; mITT and ITT populations)

Red blood cell transfusion independence n (%) [95% CI]			
	Placebo	**Lenalidomide 5 mg**	**Lenalidomide 10 mg**
mITT population	n=51	n=47	n=41
Protocol-defined (≥26 weeks)	3 (5.9) [1.2–16.2]	20 (42.6) [28.3–57.8]*	23 (56.1) [39.7–71.5]*
IWG 2000 (≥8 weeks)	4 (7.8) [2.2–18.9]	24 (51.1) [36.1–65.9]*	25 (61.0) [44.5–75.8]*
IWG 2006 (≥8 weeks)	3 (5.9) [1.2–16.2]	24 (51.1) [36.1–65.9]*	25 (61.0) [44.5–75.8]*
ITT population	n=67	n=69	n=69
Protocol-defined (≥26 weeks)	4 (6.0) [1.7–14.6]	24 (34.8) [23.7–47.2]*	38 (55.1) [42.6–67.1]•
IWG 2000 (≥8 weeks)	5 (7.5) [2.5–16.6]	33 (47.8) [35.6–60.2]*	42 (60.9) [48.4–72.4]*
IWG 2006 (≥8 weeks)	4 (6.0) [1.7–14.6]	33 (47.8) [35.6–60.2]*	42 (60.9) [48.4–72.4]*
CI = confidence interval; ITT = intention-to-treat, IWG = International Working group; mITT = modified ITT * p<0.001 versus placebo			

4.6 The manufacturer presented a sub-group analysis of erythroid response (lenalidomide 10 mg versus 5 mg). Rates of achievement of RBC transfusion independence for ≥26 week (mITT population) favoured lenalidomide 10 mg over 5 mg for most subgroups (See Figure 1 below). In 45 lenalidomide-treated patients with baseline EPO levels > 500 mIU/ml, the RBC transfusion independence rate was significantly higher with lenalidomide 10 mg than with 5 mg (76.2% versus 33.3%; p<0.004).

Figure 1. Forest plot of subgroup analysis for achievement of RBC transfusion independence for > 26 weeks in patients randomised to lenalidomide 10 mg or 5 mg (mITT population)



Key: CI = confidence interval; EPO = erythropoietin; ESA = erythropoiesis-stimulating agent; FAB = French–American–British; IPSS = International Prognostic Scoring System; LEN = lenalidomide; OR = odds ratio; RA = refractory anaemia; RAEB = RA

with excess blasts; RARS = RA with ringed sideroblasts; RBC-TI = red blood cell transfusion independence; WPSS, WHO-based Prognostic Scoring System

4.7 In the safety population, median duration of follow-up for AML progression (from date of randomisation to AML, death, or last known contact for non-AML survivors, 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, two patients (3.0%) in the placebo group, none in the lenalidomide 10 mg group and two (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 dose groups combined was 16.8% (95% CI 9.8–23.7) at two years and 25.1% (95% CI 17.1–33.1) at three years.

4.8 The median duration of overall survival follow-up in MDS-004 was 35.9 months (range 2.1–56.5 months) in the 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. At data cut-off, 101 (49.3%) patients had died, including 10 patients within 30 days of their last dose. The manufacturer stated that overall survival was similar between patients included in and excluded from the mITT population (p=0.9218). Median length of overall survival was 42.4 months in the lenalidomide 10mg group (95% CI 31.9 to not reached), ≥35.5 months in the 5mg 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 did not carry out analysis of the overall survival results with adjustment using formal statistical methods for any treatment crossover that occurred.

4.9 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 10mg group and 25% in the 5mg group, respectively. No cytogenetic responses occurred in the placebo group. Cytogenetic progression (development of new independent clones as well as additional aberrations together with del[5q]) was observed in 23.5% of patients treated with lenalidomide 10 mg (p=0.50 versus placebo), 31.3% in patients treated with lenalidomide 5 mg (p=0.17 versus 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. Among patients who achieved transfusion independence for ≥26 weeks with lenalidomide (5mg and 10 mg groups combined), onset of cytogenetic response occurred during Cycle 1 in 48.8% of patients, Cycle 2 in 37.2%, Cycle 3 in 9.3% and Cycle 4 in 4.7% of patients.

4.10 Health-related quality of life data in MDS-004 were collected for 167 patients. 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 versus –2.5; p<0.05) and 5 mg (5.9 versus –2.5; p<0.05) groups than in the placebo group.

Mixed treatment comparison

4.11 The manufacturer stated that the literature search identified only one relevant RCT of the intervention and only one small study of a

comparator treatment (best supportive care). Therefore, a mixed treatment comparison was not considered to be appropriate by the manufacturer.

Adverse events

4.12 The manufacturer reported adverse event rates for the double-blind safety population in MDS-004. A higher proportion of patients in the lenalidamide 10 mg (95.7%) and 5 mg groups (98.6%) experienced at least one 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). An overview of adverse events experienced in the double-blind safety population is presented in table 2.

Table 2. Overview of adverse events in MDS-004 study (double-blind safety population)

AE category*	Placebo (n=67), n (%)	Lenalidomide 5 mg (n=69), n (%)	Lenalidomide 10 mg (n=69), n (%)
Patients with ≥1 AE	63 (94.0)	69 (100.00)	69 (100.0)
Patients with ≥1 AE related to study drug	33 (49.3)	68 (98.6)	66 (95.7)
Patients with ≥1 NCI	29 (43.3)	62 (89.9)	65 (94.2)

CTCAE Grade 3–4 AE			
Patients with ≥1 related NCI CTCAE Grade 3–4 AE	13 (19.4)	61 (88.4)	62 (88.4)
Patients with ≥1 SAE	14 (20.9)	28 (40.6)	31 (44.9)
Patients with ≥1 SAE related to study drug	1 (1.5)	17 (24.6)	13 (18.8)
Patients with an AE leading to discontinuation of study drug	3 (4.5)	11 (15.9)	6 (8.7)
Patients with an AE leading to a dose reduction or interruption	4 (6.0)	43 (62.3)	50 (72.5)
Key: AE = adverse event; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; SAE = serious adverse event * A patient with multiple occurrences of an AE (preferred term using Medical Dictionary for Regulatory Activities version 5.2) is counted only once in the AE category			

Evidence Review Group comments

4.13 The ERG noted that, 62.3% of patients in the lenolidomide 5mg group and 72.5% in the 10mg group experienced an adverse event resulting in dose interruption or reduction. They also noted that a1 dose reduction in the lenalidomide 10 mg group meant that patients received effectively the same dose as the 5 mg group. As a

consequence, it was difficult to distinguish between the 2 lenalidomide treatment groups. The ERG noted that patients in the placebo or lenalidomide 5mg groups without minor erythroid response by week 16 or those experiencing erythroid relapse could crossover to lenalidomide 5mg or 10mg, respectively. In the placebo group, only 1 patient 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 of the short follow-up time (16 weeks) and the subsequent possibility of switching from placebo to active drug 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.

4.14 The ERG noted that data were reported for two populations in the MDS-004 study: the ITT and mITT population. The ERG also noted that confirmation of del(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 were included in the ITT population. The ERG considered that it was not clear how differences between these two populations could influence the results.

4.15 The ERG stated that most of the outcomes specified in the NICE scope were included in the MDS-004 trial and were reported in the manufacturer's submission: overall survival, progression-free survival (including time to transformation to AML or death),

response rates (including haematologic response and improvement), serious infections, adverse effects of treatment, and health-related quality of life. The ERG noted that the outcome of frequency of blood-transfusions (including blood-transfusion independence) was listed in the scope but was not reported in the manufacturer's submission.

4.16 The ERG noted that for serious infections, only grade 3 or 4 pneumonia was reported in the manufacturer's submission. The ERG noted that a clinical study report which was sent as part of the original industry submission, included reporting of infections during the double-blind treatment period (for further details, see table 4.2.1 page 46 of the ERG report).

5 Comments from other consultees

5.1 The clinical specialists stated that RBC transfusion is currently the mainstay of treatment for patients with symptomatic anaemia associated with MDS and that typically regular blood transfusions of 2-3 units of packed red blood cells per month would be required. They noted that patients with inappropriately low serum erythropoietin levels may respond to erythroid stimulating agents including recombinant erythropoietin, although the availability of this treatment varies within the UK. One specialist noted that guidelines also recommend iron chelation therapy for MDS although the evidence base for this intervention is lacking. It was also noted that allogenic stem cell transplantation is potentially curative but is not routinely offered for patients with low-risk MDS del(5q) . Similarly, azacitadine is only licensed for treating intermediate-2 and high-risk MDS. Therefore, the clinical specialists agreed that there was a high level of clinical need for lenalidomde

treatment because the only currently available treatment options for patients with low-risk and intermediate-1 MDS involve RBC transfusions.

5.2 The clinical specialists agreed that lenalidomide was a safe and effacious treatment. It was highlighted that people with TP53 gene mutation are known to have a poor response to lenalidomide, but screening for this mutation is not part of standard clinical practice. The clinical specialists did not anticipate any significant implementation issues in the use of lenalidomide for treating MDS del(5q) and agreed that treatment would be provided in secondary care because adverse events would need to be regularly monitored. Clinical specialists agreed that adverse events associated with lenalidamide could be managed by dose reduction or treatment discontinuation.

5.3 The patient experts stated that patients treated with lenalidomide would value the reduced need for blood transfusions, including a reduced risk of iron overload. Other potential benefits include fewer hospital visits and the convenience of an oral rather than an intravenous treatment. They also highlighted the advantages of lenalidomide in relieving the symptoms associated with MDS in terms of ability to work and carry out usual activities and also on their mental health. The patient experts noted that the side effects of lenalidomide treatment include reduced white cell and neutrophil count which can be treated with granulocyte colony-stimulating factor (G-CSF) injections but may be difficult for some patients to administer.

6 Cost-effectiveness evidence

6.1 The manufacturer's literature review identified 6 published cost-effectiveness studies. None of these studies were from a UK

perspective and they were not considered by the manufacturer to be relevant to the decision problem.

6.2 The manufacturer developed a de novo Markov-state-transition cost-utility model which simulated cohorts of people with low- to intermediate-1 risk MDS del(5q) receiving lenalidomide 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%.

6.3 The model structure was developed to reflect 3 key features of MDS del(5q) treatment: (i) whether the person was transfusion dependent or independent; (ii) whether the person needed iron chelation and (iii) whether the person progressed to AML. This resulted in 14 possible health states in the model including death, which are shown in figure 1. After treatment initiation, people moved to three 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 RBC transfusion. In addition, people who were transfusion dependent or independent with or without complications could develop AML (for further details, see table 3 below).

Table 3 Health state descriptions in the manufacturer's model.

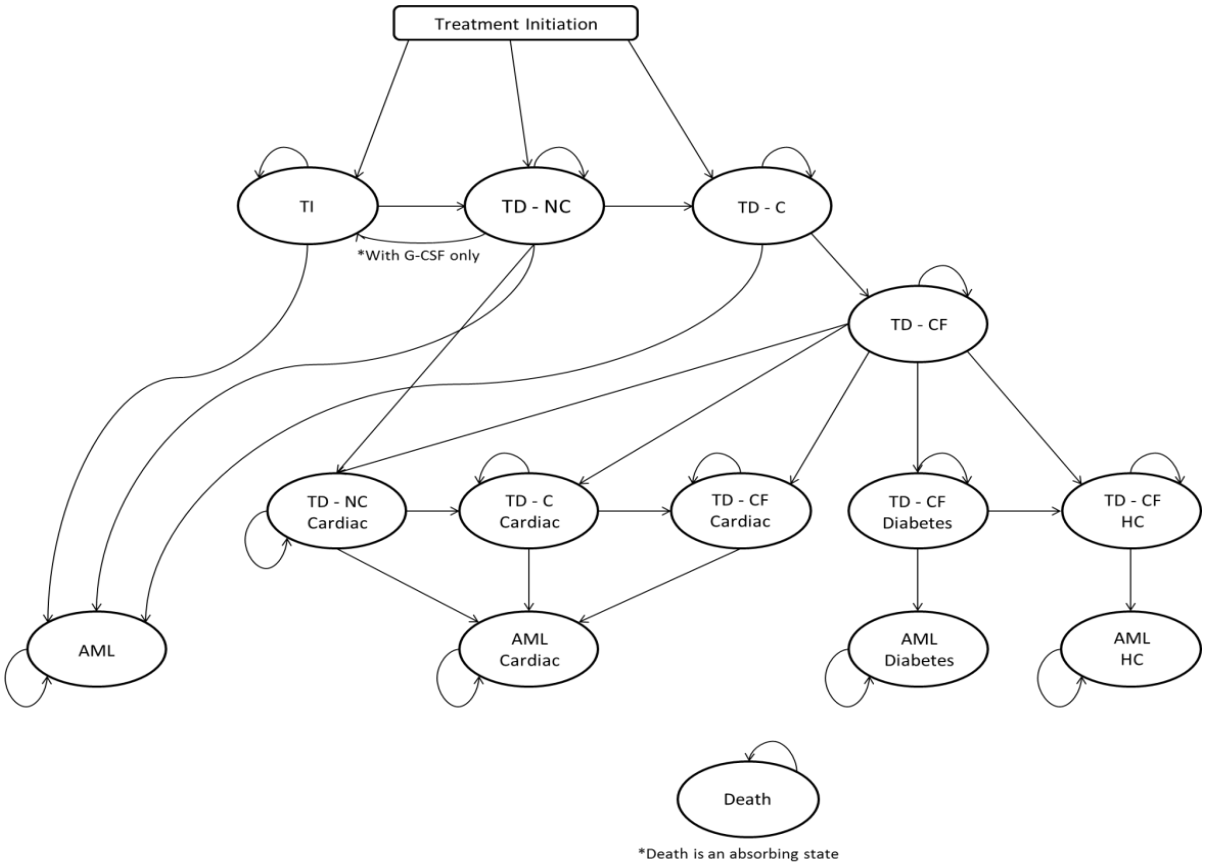
Health state	Description
TI	Transfusion independence – no requirement for red

	blood cell transfusions
TD - NC	Transfusion dependency with no requirement for iron chelation
TD-NC Cardiac	Transfusion dependency with no requirement for iron chelation and cardiac disease due to transfusion dependency
TD-C	Transfusion dependency with response to iron chelation
TD-C Cardiac	Transfusion dependency with response to iron chelation and cardiac disease due to transfusion dependency
TD-CF	Transfusion dependency with non-response to iron chelation
TD-CF Cardiac	Transfusion dependency with non-response to iron chelation and cardiac disease
TD-CF Diabetes	Transfusion dependency with non-response to iron chelation and diabetes from adverse reaction to iron overload
TD-CF HC	Transfusion dependency with non-response to iron chelation and hepatic complications from adverse reaction to iron overload
AML	Acute myeloid leukemia
AML Cardiac	AML and cardiac disease from transfusion dependency

AML Diabetes	AML and diabetes from adverse reaction to iron overload
AML HC	AML and hepatic complications from adverse reaction to iron overload
Death	Death

6.4 Clinical effectiveness data from the ITT population in the MDS-004 study were used in the model. The manufacturer's stated that this population more closely matched the NICE scope than the mITT population. It was also stated that the mITT population substantially reduced the amount of available data and that no significant differences were observed in key endpoints between trial arms in MDS-004. The dosing schedule for people 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 people in the lenalidomide group remained on treatment until they stopped responding to treatment (i.e. became transfusion dependent). Best supportive care was based on the placebo arm of the MDS-004 study which included the provision of blood transfusions for transfusion dependent patients. The manufacturer stated that, in UK clinical practice, best supportive care may also include the provision of an erythropoiesis stimulating agent (ESA). Therefore, the manufacturer assumed that 28% of people 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 people who did not respond to an ESA as part of best supportive care would receive an additional G-CSF for 3 cycles.

Figure 2: Model structure as provided by the manufacturer.



TI = transfusion independent, TD = Transfusion dependent, NC = No chelation, C = Chelation, CF = Chelation Failure, Cardiac = cardiac disease, Diabetes = Diabetes, AML = acute myeloid leukaemia, HC = Hepatic conditions.

6.5 The proportion of people who responded to treatment (i.e. who became transfusion independent for 56 consecutive days) was derived from the MDS-004 trial ITT population. The response rates were 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 were taken from a separate study that reported response rates after combination therapy according to predictive groups (Jadersten et al. 2005). The manufacturer estimated a weighted response rate to an ESA and G-CSF of 21.7% for people with a high and intermediate probability of response. 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 would be half of those to combination therapy, response rates of 10.8% for ESA monotherapy and G-CSF when added to ESA monotherapy.

6.6 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 determine whether there was a significant difference in response duration depending on treatment being 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) who 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 determined using the Integrated

Brier Score (IBS) and Akaike Information Criterion (AIC), the lognormal distribution was used to estimate both response duration curves.

6.7 The manufacturer included 2 adverse events in the model, grade 3 or 4 neutropenia and thrombocytopenia, 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 neutropenia and thrombocytopenia events could be attributed to lenalidomide treatment because MDS is characterized by these peripheral cytopenias. Therefore, the number of patients who experienced neutropenia and thrombocytopenia in the lenalidomide group was adjusted by subtracting the patients who experienced these events in the placebo group. The manufacturer assumed that any adverse events in the lenalidomide group occurred in the first 4 cycles of the model. On the basis of data from MDS-004, the manufacturer assumed that only a proportion of people who experienced 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.

6.8 The model accounted for 2 periods of treatment interruption during which people 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 people in the lenalidomide group experienced a first dose interruption and 73.8% experienced a second dose interruption. The mean duration of 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 duration of 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.

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

6.10 The manufacturer assumed that iron chelation therapy was initiated for people who were in the transfusion dependent states in order to avoid complications associated with iron overload. It was assumed that people started iron chelation therapy when they reached a threshold of 25 RBC units in the model. A response rate for iron chelation of 66% was taken from a study by Kontoghiorges et al. (2000). Response and non-response to iron chelation therapy was assumed to occur in the first cycle of treatment. People who needed iron chelation moved to either the chelation or chelation-failure state depending on their response to iron chelation therapy. It was 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, taken from a study by Jaeger et al. (2008). The probabilities of developing diabetes mellitus and hepatic complications per 28-day cycle were 0.21% and 0.66%, respectively.

6.11 People in the model were assumed to be at risk of developing AML. The time to development of 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 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 del(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'.

6.12 The manufacturer stated that survival in patients with MDS is significantly related to transfusion dependency. Therefore, 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 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 reported median survival for the combined MDS-003 and MDS-004 trials of 3.8 years.

6.13 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, 35 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 values resulted in an unacceptable level of error. Therefore, the 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. The manufacturer chose utility values taken from a published study of people with MDS (Szende et al., 2009) because they were closest to the NICE reference case. In this study, utility data were collected from a sample of 47 MDS patients (including 21 from the UK) using visual analogue scale (VAS) and time trade-off (TTO) methods. Patients were interviewed to elicit utility values for transfusion independence, and transfusion dependence. The resulting mean utility values for the UK sample using the TTO method, were: transfusion independence (0.85), transfusion dependence (0.65). The study did not include AML as a separate health state. Therefore, the manufacturer assumed that people in the AML state had a utility value of 0.65.

6.14 Utility decrements associated with chelation therapy (21% for DFO and 0% for oral chelator use) 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 Fryback (1993) and Wong (1995).The model did not incorporate utility decrements for patients who experienced neutropenia and thrombocytopenia. The manufacturer's justification was these adverse events have a short term effect on quality of life.

6.15 The manufacturer’s model included drug acquisition, monitoring costs and costs of adverse events. Costs of lenalidomide were based on the dosing observed in the MDS-004 trial, which involved treatment interruption because of adverse events, after which the dose would be adjusted downwards (initial dose: 10mg per day for 21 days per 28 day cycle; first reduction: 5mg per day 28 days per cycle; second reduction: 5mg per day every other day). In addition, monitoring costs, transfusion costs, chelation costs, costs of treating AML and costs of complications and adverse events were included. Drug acquisition prices were obtained from the British National Formulary (edition 64). To estimate the costs of iron chelation therapy, the ERG assumed that people had either desferroxamine (29%) or deferasirox (71%) based on prescription cost analysis data for England (2010). The cost of intravenous desferroxamine was estimated using the average patient weight from the MDS-004 trial of 69 kg. The frequency of monitoring associated with the initiation of lenalidomide treatment was taken directly from the summary of product characteristics: GP visits (and blood counts) occurred weekly for the first eight weeks, bi-weekly for the next four weeks and then four-weekly thereafter (at this point they are being monitored at the same frequency as patients who are not receiving treatment). For best supportive care, monitoring was assumed to occur once per cycle throughout treatment.

Table 4 Summary of resources and costs estimates used in the manufacturer's economic model (Table 5.13 ERG report page 85)

Item	Standard Unit	Unit Price	Source
Drug Cost			
Lenalidomide	per 10mg tablet	£180.00	BNF 64th ed.
Lenalidomide	per 5mg tablet	£170.00	BNF 64th ed.
ESA Erythropoeitin (Eprex)	per 20,000 IU vial	£110.62	BNF 64th ed.
G-CSF (Neupogen)	per 300 mg vial	£52.71	BNF 64th ed.
Chelation therapy			
IV iron chelation	per dose	£25.35	BNF 64th ed.
Oral iron chelation	per dose	£46.37	BNF 64th ed.
Monitoring costs			
GP Visit	Per visit	£36.00	PSSRU 2011 GP surgery cost including qualifications
Full Blood Count	Per test (one per visit)	£3.09	NHS 2011/12 reference costs haematology
Serum Ferritin	Per test (one per visit)	£1.23	NHS 2011/12 reference costs biochemistry
Blood transfusion cost			
RBC unit		£367.98	Davies (2006)
Platelet transfusion		£312.49	Guest (1998)
AML treatment			
AML treatment	per 28 days	£1,919.40	STA Azacitidine
Transfusion dependent complications			
Cardiac Disease	annual cost	£3,792.30	Luengo-Fernandez et al
Hepatic Complications	annual cost	£1,445.80	Wright (2006)
Diabetes Mellitus	annual cost	£ 3,644.40	Kavanos (2012)
Adverse events lenalidomide			
Thrombocytopenia	per episode	£1,636.38	NHS 2011/12 reference costs
Neutropenia	per episode	£1,636.38	NHS 2011/12 reference costs

Table 5 Drug treatment costs per cycle

	Total cost e.g.

	per cycle, per patient
Lenalidomide 10mg 21 days per cycle	£3,780
Lenalidomide 5mg 28 days per cycle	£4,760
Lenalidomide 5mg 14 days per cycle	£2,380
ESA (2 vials per week)	£885
G-CSF (3 vials per week)	£633

6.16 The manufacturer's base-case deterministic cost-effectiveness analysis resulted in an incremental cost-effectiveness ratio (ICER) of £56,965 for lenalidomide compared with best supportive care (incremental costs £50,652; incremental QALYs 0.89). The probabilistic cost-effectiveness analysis resulted in an ICER of £58,178 per QALY gained.

Table 6 Base case cost-effectiveness results for lenalidomide compared with best supportive care

Technology	**Total costs**	**Total QALYs**	**Incremental costs**	**Incremental QALYs**	**ICER**
Best supportive care	£105,726	2.58			
Lenalidamide	£156,308	3.46	£50,582	0.89	£56,965
ICER; incremental cost-effectiveness ratio, QALY; quality-adjusted life year.					

6.17 The manufacturer undertook a series of deterministic sensitivity analyses on various model parameters. The key driver of the cost-effectiveness estimate of lenalidamide compared with best supportive care was the utility value for the transfusion independent state (see figure 3). The ICER was also sensitive to the parameters used for mortality and AML. The manufacturer also conducted a range of scenario analyses (see table 8 below). The results of these scenario analyses indicated that 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 a study by Goss et al. (2006) of US patients with low and intermediate-1 risk MDS del(5q), this resulted in an ICER of £47,621 per QALY gained. Results of the probabilistic sensitivity analysis showed that, at a cost-effectiveness threshold range of £20,000 to £30,000 per QALY gained; lenalidomide had a 0% probability of being cost effective.

Figure 3 Top 10 parameters affecting the ICER

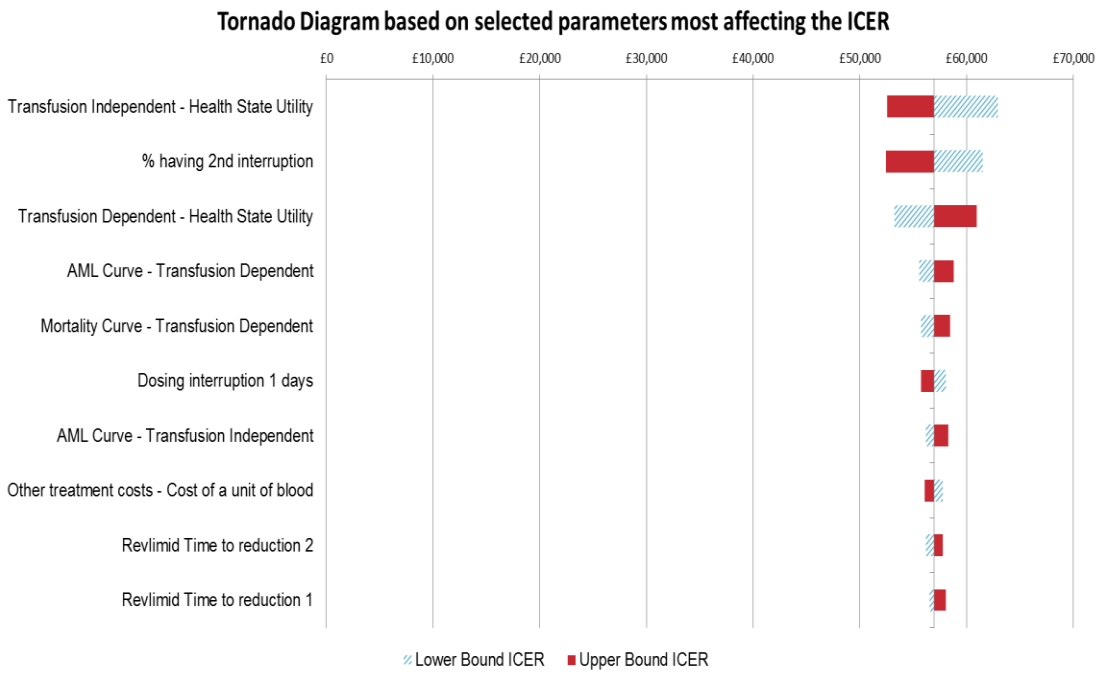


Table 7 Results of the manufacturer's scenario analysis

Parameter	Base case	Scenario analysis	ICER
Base Case			£56,965
Population used for parameter estimation	UK patients	All trial patients	£59,500

Comparator	Blood transfusion + 28% of patients ESA	All patients ESA All patients only blood transfusion	£56,623 £58,913
Iron chelation threshold	25	20 30	£55,953 £57,761
Source utilities	Szende	Goss Buckstein	£47,621 £59,323
Method of extrapolation response duration	Lognormal	Exponential Weibull Log-logistic Extreme value	£56,265 £56,403 £56,730 £55,445
Method of extrapolation AML progression	Weibull	Exponential Log-logistic Lognormal Extreme value	£56,717 £56,237 £55,514 £57,703
Method of extrapolation overall survival	Weibull	Exponential Log-logistic Lognormal Extreme value	£56,646 £55,813 £55,536 £58,117

Evidence Review Group comments

6.18 The ERG considered 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 and the model structure in the electronic model did not fully match. The ERG 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 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 length of 28 days was rather long.

6.19 The ERG noted that in the manufacturer's economic model, best supportive care was defined as the provision of 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 occur. 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.

6.20 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. The ERG noted that, according to expert opinion (Personal communication, Dr Culligan, 23 February 2013), there is some uncertainty about the effect of providing ESA to MDS del(5q) patients. 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 manufacturer confirmed that these were programming errors. After correcting for these errors, the ICER for lenalidomide compared with best supportive care increased to £58,732 per QALY gained. 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.

6.21 The ERG noted that another key driver of the cost effectiveness of lenalidomide was the proportion of people who had a second treatment interruption in the model. The ERG acknowledged that these values were directly obtained from the MDS-004 trial, but only cost estimates were assumed to be affected by treatment interruptions in the model, and the clinical effectiveness of lenalidomide remained constant. The ERG judged that in clinical practice, treatment interruptions would affect the response rate of lenalidomide.

6.22 The ERG noted that the utility values taken from the Szende study did not conform to the NICE reference case because they were obtained from UK MDS patients rather than a sample of the public. The ERG considered that the health state descriptions in the Szende study were very broad, and therefore the transfusion dependent state may already incorporate 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 people in the transfusion dependent state may favour lenalidomide because people in the best supportive care group spent 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.

6.23 The ERG identified several issues in relation to the cost estimates used in the manufacturer's model. The ERG noted that people receiving iron chelation therapy in the model either had desferroxamine (DFO) or deferasirox based on prescription cost analysis data in England from 2010. The ERG considered that deferiperone, which is a third possible iron chelation therapy listed in the prescription cost analysis, should also have been included. When the ERG included deferiperone 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 £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 (£1686.38) 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% of the mean estimate would be more reasonable. Similarly, the ERG noted that the probabilistic sensitivity analysis did not account for uncertainty around the number of monitoring visits in both treatment groups.

6.24 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 was updated to £1332 per cycle to include deferiperone
- Treatment costs of AML were updated £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 (£1045) and thrombocytopenia (£1768) were changed
- Uncertainty around the number of monitoring visits and uncertainty increased around cost estimates complications and adverse events were incorporated

6.25 Table 6.1 on page 105 of the ERG report shows the impact of each of these individual changes on the cost effectiveness estimate. When the ERG included all of these changes on the manufacturer's model the deterministic cost-effectiveness analysis resulted in an incremental cost-effectiveness ratio (ICER) of £62,674 for lenalidomide compared with best supportive care (incremental costs £50,898; incremental QALYs 0.84). The corresponding probabilistic cost-effectiveness analysis resulted in an ICER of £65,052 per QALY gained.

Table 8 ERG base case cost-effectiveness results for lenalidomide versus best supportive care

Technology	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
Without PAS					
Best supportive care	£102,856	2.64			

Lenalidamide	£153,733	3.45	£50,898	0.84	£62,674
ICER; incremental cost-effectiveness ratio, QALY; quality-adjusted life year.					

6.26 The ERG reproduced the manufacturer's sensitivity and scenario analyses in the amended model. The sensitivity analyses found that the key drivers of the cost-effectiveness estimate of lenalidomide compared with best supportive care were the utility values for the transfusion independent state and the response rate for the lenalidomide treatment group. The results of the scenario analyses indicated that the ICERs were robust to nearly all of the scenarios explored except when alternative utility values taken from a study by Goss et al. (2006) were used, which resulted in an ICER of £51,956 per QALY gained (for further details see pages 98-99 of the ERG report).

6.27 The ERG undertook an additional series of scenario analyses, which are presented in table 9 below. The factor which had the most significant effect on the ICER was the utility value for transition dependence. When the utility value for transfusion dependence was increased from 0.65 to 0.77 (the value for reduced transfusion burden in Szende 2009), the resulting ICER was £68,357 per QALY gained.

Table 9 Additional scenarios on the ERG base case explored by the ERG

Parameter	ERG Base case	Scenario analysis	ICER
ERG Base case			£62,674
Utility value for transfusion dependence	Utility value fully transfusion dependent (0.65)	Utility value reduced transfusion burden (0.77)	£68,357
Utility value for AML	Utility AML is similar to transfusion dependence (0.65)	Utility of AML is reduced with 25% (0.49)	£62,753

Cost adverse events	Treatment cost adverse events	Zero cost for treating adverse events	£62,448
Treatment of adverse events	Only a proportion of patients experiencing AEs require treatment	All patients experiencing AEs require treatment	£62,846
Monitoring	Monitoring visits at GP	Monitoring visits at haematologist	£64,079
Cycles before Chelation Threshold reached (non-responders)	2	4	£67,428
Proportion of patients treated with IV chelation	5.70%	100%	£56,750
Response duration BSC	According to 5mg	According to 10mg	£64,164
Utility decrement AE	0% Thrombocytopenia 0% Neutropenia	25% Thrombocytopenia 25% Neutropenia	£63,893

7 Equalities issues

7.1 The manufacturer stated that MDS predominantly affects elderly patients, many of whom have concomitant conditions. and mobility issues; that is, patients who are frail and live at long distances from a hospital may find difficulty in travelling to receive blood transfusions. The manufacturer also stated that lenalidomide is an oral therapy, which can be taken at home, thus ensuring equality of access. A statement from a clinical specialist received during consultation stated that, as lenalidomide cannot be administered to pregnant women or those who are trying to conceive, this may result in inequitable access to treatment. No other relevant equalities issues were identified in the evidence submitted.

8 Innovation

8.1 The manufacturer stated that, because lenalidomide is administered orally and the fact that this is the first treatment in an

area of high unmet need, makes it an innovative treatment option for people with MDS del(5q).

9 Authors

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with input from the Lead Team (Peter Selby, Alan Haycox and Emily Lam).

Appendix A: Supporting evidence

Related NICE guidance

Published

- 'Improving outcomes in haemato-oncology cancer'. NICE cancer service guideline CSGHO (2003). Available from www.nice.org.uk/guidance/CSGHO
- Azacitidine for the treatment of myelodysplastic syndrome, chronic myelomonocytic leukaemia and acute myeloid leukaemia. NICE technology appraisal guidance 218 (2011). Available from www.nice.org.uk/guidance/TA218