NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Lenalidomide for treating multiple myeloma after 1 prior treatment with bortezomib

The Department of Health has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using lenalidomide in the NHS in England. The appraisal committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, clinical experts and patient experts.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the consultees and commentators for this appraisal and the public. This document should be read along with the evidence (see the committee papers).

The appraisal committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The appraisal committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the committee will also consider comments made by people who are not consultees.
- After considering these comments, the committee will prepare the final appraisal determination (FAD).
- Subject to any appeal by consultees, the FAD may be used as the basis for NICE's guidance on using lenalidomide in the NHS in England.

For further details, see NICE's guide to the processes of technology appraisal.

The key dates for this appraisal are:

Closing date for comments: 2nd December 2016

Fifth appraisal committee meeting: To be confirmed

Details of membership of the appraisal committee are given in section 6.

1 Recommendations

1.1 Lenalidomide in combination with dexamethasone is not recommended for treating multiple myeloma in adults:

- whose condition has relapsed for the first time
- who have had 1 prior treatment with bortezomib
- when thalidomide is contraindicated or not suitable and
- when stem cell transplantation is not suitable.

1.2 This guidance is not intended to affect the position of patients whose treatment with lenalidomide was started within the NHS before this guidance was published. Treatment of those patients may continue without change to whatever funding arrangements were in place for them before this guidance was published until they and their NHS clinician consider it appropriate to stop.

2 The technology

Description of the technology	Lenalidomide (Revlimid, Celgene) is a derivative of thalidomide and has immunomodulatory, antineoplastic, anti-angiogenic and pro-erythropoietic activity. It is administered orally.
Marketing authorisation	Lenalidomide in combination with dexamethasone has a marketing authorisation for treating 'multiple myeloma in adult patients who have received at least one prior therapy.'
Adverse reactions	The summary of product characteristics includes the following adverse effects for lenalidomide: neutropenia, anaemia and thrombocytopenia. Because lenalidomide is structurally related to thalidomide, a known human teratogen that causes severe birth defects, 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.
Recommended dose and schedule	The recommended starting dosage is 25 mg orally once daily on days 1–21 of repeated 28-day cycles.
Price	Lenalidomide is available as a 21-capsule pack. The cost per pack varies according to capsule size: £3,570 (5 mg), £3,780 (10 mg), £3,969 (15 mg) and £4,368 (25 mg; excluding VAT; British national formulary online, accessed October 2016).
	The company (Celgene) has agreed a complex patient access scheme with the Department of Health. If lenalidomide had been recommended, the cost of lenalidomide for people remaining on treatment for more than 26 cycles would have been met by the company. The Department of Health considered that this patient access scheme would not constitute an excessive administrative burden on the NHS.

3 Evidence

This is a partial review of technology appraisal 171. The appraisal committee (section 6) considered evidence submitted by Celgene and a review of this submission by the evidence review group (ERG). During the development of this appraisal, the company submitted documents with additional evidence; each document was critiqued by the ERG. See the committee papers for full details of the evidence.

4 Committee discussion

The appraisal committee reviewed the data available on the clinical and cost effectiveness of lenalidomide, having considered evidence on the nature of multiple myeloma and the value placed on the benefits of lenalidomide by people with the condition, those who represent them, and clinical experts. It also took into account the effective use of NHS resources.

4.1 The committee heard about the experience of patients with multiple myeloma. It heard from a clinical expert that survival rates have improved since the introduction of thalidomide, bortezomib and lenalidomide, but that multiple myeloma remains an incurable disease. The committee understood that, for the relevant group of patients who had initial treatment with bortezomib, there are limited treatment options after first relapse. It heard from clinical and patient experts that lenalidomide plus oral dexamethasone would be a useful treatment option. The committee also heard that, in the opinion of the patient expert, using lenalidomide plus dexamethasone earlier in the treatment pathway may provide more benefit than using it later. The committee recognised that patients value oral treatments such as lenalidomide plus dexamethasone because some people find it difficult to travel to hospital for repeated treatment with intravenous or subcutaneous therapies. The committee concluded that patients and clinicians would like to have the option of treatment with lenalidomide.

Treatment pathway and comparators

4.2 The committee considered the treatment pathway for people with multiple myeloma and acknowledged that this would differ depending on whether a person's disease is suitable for stem cell transplantation or not. The committee agreed that the population relevant to this appraisal is people for whom stem cell transplantation is not suitable. The committee further agreed that the relevant population is people for whom first-line

thalidomide is contraindicated, and who therefore have had 1 prior treatment with bortezomib. It heard from a clinical expert that, although lenalidomide and thalidomide are structurally similar, some people cannot have thalidomide but can have lenalidomide. The committee acknowledged that, in the opinion of clinical and patient experts, the preferred option for many of these patients is lenalidomide plus dexamethasone. The committee was also aware that lenalidomide for multiple myeloma had been removed from the Cancer Drugs Fund.

4.3   The committee discussed the 3 comparators in the scope:

- Bortezomib retreatment. At previous meetings (from February 2014 to April 2016) the committee heard from a clinical expert that bortezomib retreatment was offered to NHS patients with disease suitable for this treatment. It noted that bortezomib retreatment had been removed from the Cancer Drugs Fund in January 2015. At the final committee meeting (October 2016), the committee heard that NHS England had advised NICE that it would no longer commission bortezomib retreatment. The committee concluded it was no longer a comparator.
- Cytotoxic chemotherapy, for example melphalan. The committee heard from the clinical experts that, in the absence of lenalidomide, cytotoxic chemotherapy was a treatment option after first relapse. It concluded that cytotoxic chemotherapy was a comparator.
- Bendamustine, which is available via the Cancer Drugs Fund. The committee heard from clinical experts that they prefer to use bendamustine later in the treatment pathway as the fourth or fifth treatment. It concluded that bendamustine was not a comparator.

The committee asked the company whether dexamethasone monotherapy (the comparator in the lenalidomide trials, see section 4.5) was used in the NHS for patients relevant to this appraisal. It heard from the company that patients often have corticosteroids as part of their first treatment, and that clinicians do not usually offer dexamethasone alone

as a second treatment. The committee heard from both the company and clinical experts that dexamethasone monotherapy was not used in the NHS and so concluded it was not a comparator. It concluded that the only current treatment option in the NHS for the population relevant to this appraisal was cytotoxic chemotherapy.

Clinical effectiveness

4.4 The company did not identify any randomised controlled trials that compared lenalidomide with cytotoxic chemotherapy. For lenalidomide, the company presented a pooled analysis of 2 randomised controlled trials, MM-009 and MM-010 (see table 1). For melphalan chemotherapy, the company presented data from a small single-arm trial (Petrucci et al. 1989).

Table 1 Summary of clinical studies

Study characteristics	Pooled MM-009 and MM-010 trials		Petrucci et al. (1989)
Study design	Multinational randomised controlled trial		Single-arm trial
Patients in the trial	About 35% of patients had 1 prior therapy and about 65% had had at least 2 prior therapies.		Patients had disease that had relapsed or was refractory to chemotherapy. The number of prior therapies was not reported.
Sample size	353	351	34
Intervention	Lenalidomide plus dexamethasone	Placebo plus dexamethasone	Melphalan plus prednisolone
Median progression-free survival (months)	11.1	4.6	Not reported
Median overall survival (months)	38.0	31.6	8.0

Lenalidomide plus dexamethasone compared with placebo plus dexamethasone

4.5 The committee agreed that MM-009 and MM-010 had shown that lenalidomide plus dexamethasone was more effective than placebo plus dexamethasone for extending progression-free and overall survival (see

table 1). However, it recognised that dexamethasone alone was not a relevant comparator in this appraisal. The committee also recognised that the population in the trials did not match the population for this appraisal because:

- only 2 out of 353 patients in the lenalidomide group had received 1 prior treatment with bortezomib
- the trials' inclusion criteria did not specify that thalidomide treatment was inappropriate, contraindicated or could not be tolerated
- the trials' patients were younger than the multiple myeloma population addressed in this appraisal
- the trials included a high proportion of patients who had had 2 or more prior therapies.

The committee heard from the clinical expert that, based on their experience, the results from MM-009 and MM-010 were generalisable to the population of interest despite the differences. It concluded that, for treating multiple myeloma in the population relevant to this appraisal, lenalidomide plus dexamethasone was more effective than dexamethasone alone.

Lenalidomide plus dexamethasone compared with cytotoxic chemotherapy

4.6   The committee was aware that the company estimated the effectiveness of cytotoxic chemotherapy using data from a small single-arm trial without a control group. The committee noted that a crude comparison suggested that median survival times were substantially longer for patients having lenalidomide than for patients having cytotoxic chemotherapy (see table 1). The committee had concerns about confounding, and it was aware that this non-randomised comparison was at high risk of bias. It also understood that the patients in Petrucci et al. were having chemotherapy for a second time, which may be less effective than chemotherapy the first time. The committee heard from clinical experts that, despite the lack of

robust evidence, in their experience lenalidomide plus dexamethasone was more effective than cytotoxic chemotherapy. It agreed that the evidence was very uncertain, but noted the significant size of effect in favour of lenalidomide plus dexamethasone shown by the difference in survival times, and the opinion of several clinical experts. The committee therefore concluded that lenalidomide plus dexamethasone was likely to be more effective than cytotoxic chemotherapy for treating multiple myeloma in the population relevant to this appraisal.

Cost effectiveness

4.7   This section describes the committee's consideration of the company's modelling submitted in February and June 2016, rather than the modelling submitted before this. The company used 'multistate' modelling because it meant that the survival curves for progression-free and overall survival did not cross (this had been a problem in previous versions of the model). Both the February and June 2016 models compared lenalidomide plus dexamethasone with melphalan chemotherapy plus prednisolone, in the population relevant to this appraisal. The February 2016 version of the model was based on a crude indirect comparison with the Petrucci et al. (1989) study of melphalan; the committee's consideration of this model version is described in sections 4.9 to 4.13. The June 2016 version of the model used direct trial data from MM-009 and MM-010 and assumed that melphalan had the same clinical effectiveness as dexamethasone. The committee's consideration of the June 2016 model version is described in sections 4.14 to 4.16. The committee used the June 2016 model for decision making. The committee's discussion of previous model versions is described in the second appraisal consultation document.

Company's approach to modelling lenalidomide plus dexamethasone

4.8   The committee discussed the company's method for predicting progression-free and overall survival with lenalidomide plus dexamethasone, noting that the company used data from the lenalidomide

groups of MM-009 and MM-010. It understood that, in both the February and June 2016 models, the company chose a multistate-modelling approach to calculate the probability of moving between model states. The committee noted that the lenalidomide trials had a maximum follow-up of 4.6 years. It agreed that there was uncertainty about outcomes in the extrapolated portion of the survival curves, which covered a further 20 years. To reduce this uncertainty, the committee would have preferred to have seen longer-term survival data, but it heard that the company was no longer collecting data from MM-009 and MM-010. The committee also heard from the clinical experts that the company's predicted survival times with lenalidomide seemed reasonable. It concluded that while there was some uncertainty about long-term outcomes with lenalidomide, multistate modelling was an improvement over the previous methods used by the company.

Crude indirect comparison with melphalan

4.9　The company's model from February 2016 used observational data from Petrucci et al. (1989) to estimate the effectiveness of melphalan. The committee agreed that there were 4 fundamental problems with the company's model based on a crude indirect comparison:

- it was at high risk of bias (section 4.6)
- the melphalan data came from only 34 patients (section 4.4)
- the statistical techniques may not have been technically correct (section 4.10)
- the model predictions lacked external validity (sections 4.11 and 4.12).

The committee concluded that the model based on a crude indirect comparison was not suitable for decision-making.

4.10　The company calculated a crude hazard ratio by taking the ratio of median survival times with melphalan compared with lenalidomide (estimated from MM-009 and MM-010). It then applied this hazard ratio to the multistate model predictions for patients having lenalidomide to predict

progression-free and overall survival with melphalan. The committee had 2 major concerns about this approach to modelling:

- The model was based on a crude indirect comparison using non-randomised data, meaning there was a high risk of bias (see section 4.6).
- Calculating hazard ratios using medians is only technically correct when using an exponential distribution to extrapolate outcomes. The model did not use a single exponential distribution; instead, it used a multistate model that is similar to several exponential distributions fitted to different time periods. In its response to the committee's request for additional evidence, the company accepted that its method had limitations, and explained that a single exponential curve did not fit the data well for lenalidomide.

The committee concluded that the company's model based on a crude indirect comparison was at high risk of bias and relied on statistical techniques that are not technically correct.

4.11   The committee considered the company's approach to modelling subsequent treatments (that is, third- and fourth-line therapies) after relapsing on second-line treatment. The committee agreed it was important to consider subsequent treatments and to include both their costs and effectiveness in the model. It noted that the company's February 2016 model assumed that all patients having melphalan would go on to have third-line lenalidomide; for this reason, the company extended the survival times for melphalan patients to reflect the benefit of third-line treatment. The committee expressed concerns that including third-line lenalidomide in the comparator arm had produced implausible results. The company agreed that there were illogical results, but only when the model used bortezomib as a comparator, and said that this was not the case for the comparison with melphalan. In contrast, the evidence review group (ERG) advised that the results for bortezomib (even though

the committee no longer consider it a comparator) suggested that the method for adjusting for subsequent treatments was unsuitable and should not be used. The committee concluded that the company's model based on a crude indirect comparison was limited because the adjustment for subsequent treatments gave illogical results.

4.12 The committee had further concerns about the external validity of the model. This was because the model predicted a mean survival benefit of 2.7 years for lenalidomide plus dexamethasone compared with melphalan, whereas MM-009 and MM-010 showed a median survival benefit of only 6.4 months for lenalidomide plus dexamethasone compared with dexamethasone. The committee was concerned that these results were not plausible because, based on clinical advice, it expected the survival benefit versus melphalan to be similar to or greater than the survival benefit versus dexamethasone monotherapy. To explore this issue further, the committee asked the company to use its model to predict survival times with dexamethasone alone. Although dexamethasone was not a comparator, the committee used this analysis to assess the external validity of the model. The company's model predicted that the mean survival time for patients having dexamethasone (informed by MM-009 and MM-010) was 4.9 years, compared with only 3.2 years with melphalan (informed by Petrucci et al. 1989). In this analysis, the committee noted that the company assumed that only 48% of patients on dexamethasone had third-line lenalidomide (informed by MM-009 and MM-010) but that all patients on melphalan had third-line lenalidomide which was expected to increase survival times. The committee agreed that these results were not plausible; based on clinical advice, it expected survival times with melphalan to be similar to or better than with dexamethasone. The committee concluded that the company's model based on a crude indirect comparison lacked external validity.

4.13 The committee discussed the long-term survival benefit of lenalidomide plus dexamethasone compared with melphalan in the company's model

based on a crude indirect comparison. It noted that the company applied the hazard ratios throughout the model, which implied that the relative survival benefit of lenalidomide continued after patients stopped treatment. The committee was concerned that there was no evidence of an ongoing survival benefit after patients stopped treatment. The committee was aware of scenarios from the company and the ERG that explored different assumptions about long-term survival. However, it did not identify a preferred scenario because it had concluded that this approach to modelling was not suitable for decision-making.

Assuming equivalence between melphalan and dexamethasone

4.14 In June 2016, the company submitted an alternative approach to modelling, using the same model structure but assuming that melphalan had the same clinical effectiveness as dexamethasone. In the analyses assuming equivalence of melphalan to dexamethasone, the company used data from the dexamethasone group of MM-009 and MM-010 to predict clinical outcomes with melphalan. The company, ERG and committee agreed that this approach to modelling offered several advantages over the previous approach using a crude indirect comparison (see sections 4.9 to 4.13). Specifically, the analyses assuming equivalence:

- used a large, randomised data set; this meant the comparison was at low risk of bias
- accurately captured the impact of third-line lenalidomide in the melphalan arm because 48% of patients in the dexamethasone group had subsequent lenalidomide in MM-009 and MM-010; this meant it was not necessary to adjust the comparator arm to reflect the benefit of third-line lenalidomide
- did not need hazard ratios to be calculated using median survival times because patient-level data for both arms of the model were available from MM-009 and MM-010.

The ERG noted that it did not have access to the Kaplan–Meier data for patients having dexamethasone second-line in MM-009 and MM-010. So, it was unable to assess whether the model predictions were a good fit to the mortality data from the trials. The committee agreed that this added uncertainty to the analysis. While acknowledging this shortcoming, for the reasons listed above, the committee concluded that the analysis assuming equivalence was preferable to the previous approach based on a crude indirect comparison.

4.15   The company stated that the assumption of equivalence was supported by a randomised controlled trial comparing 4 treatments including melphalan plus prednisolone and dexamethasone in patients who had not had previous treatment (Facon et al. 2006). The study showed no difference in overall survival (the primary endpoint) between dexamethasone and melphalan. The committee was not convinced that melphalan had the same clinical effectiveness as dexamethasone because Facon et al. showed that progression-free survival was longer with melphalan. It was also aware that the study did not recruit enough patients, based on the sample size calculations, to detect a difference in survival. It again noted that melphalan, but not dexamethasone alone, was used in clinical practice in the NHS. Clinical opinion suggested that melphalan might be more effective, in which case the analysis assuming equivalence would be biased in favour of lenalidomide plus dexamethasone. The committee concluded that the analysis assuming equivalence may have underestimated the incremental cost-effectiveness ratio (ICER) for lenalidomide compared with melphalan.

4.16   The ERG identified a substantial error in calculating the acquisition cost of melphalan in the June 2016 version of the model. Correcting the error increased the company's base-case ICER from £20,000 to £46,000 per quality-adjusted life year (QALY) gained. The committee heard that the company agreed with the ERG's correction. This document presents corrected ICERs.

Progression-free survival in analyses assuming dexamethasone is equivalent to melphalan

4.17   The ERG observed that, in the modelling of progression-free survival with dexamethasone (which was a proxy for melphalan), the company's extrapolation had a 'long tail'. This meant that some patients survived for several years without their disease progressing. The ERG advised that this extrapolation was implausible. Its analyses used the company's progression-free survival curve for the first 1.5 years but, after that time, the ERG chose an exponential distribution. The committee found it difficult to identify a preferred extrapolation curve because it did not have access to the Kaplan–Meier curves from the trial that showed the number of patients at risk. Without this information, its best estimate was that the true curve was likely to be somewhere between the company's and ERG's approaches. The committee also noted that the model was not very sensitive to the choice of curve for progression-free survival: using the ERG's curve increased the company's base-case from £46,000 to £48,000 per QALY gained.

Cost of lenalidomide

4.18   The committee discussed the modelled costs of lenalidomide plus dexamethasone, noting that the company's model capped the drug costs at 26 cycles to reflect the complex patient access scheme. The committee queried why the company had not included any costs for administering the patient access scheme. It heard that the NHS already had procedures in place for monitoring treatment duration with lenalidomide to support the pregnancy prevention programme and the existing patient access scheme (for patients who have had 2 previous treatments). The committee heard from the clinical expert that expanding the lenalidomide patient access scheme to include patients who had had 1 previous treatment would not markedly increase the administration costs. The committee concluded that the company had modelled lenalidomide costs appropriately.

Utilities

4.19   The committee discussed the company's choice of utility values. It noted that the company took EQ-5D utility values from a model by van Agthoven et al. (2004). The original source of these utility values was a 2002 PhD thesis which, to the committee's knowledge, had not been published in a peer-reviewed journal when discussed at the committee's first meeting. The committee also noted that the utility values were derived from a population younger than the population in this appraisal, and the values were higher than the average population of the same age. In addition, the company took the utility decrements for adverse events from several different sources, which used different methods, were from other countries and included people with different types of cancer. The committee concluded that there was a limited evidence base to support the utility values and this added to the uncertainty in the model.

Results of cost-effectiveness analyses

4.20   The committee's preferred analysis, acknowledging shortcomings, assumed that melphalan had the same clinical effectiveness as dexamethasone. Under this assumption, the company's ICER for lenalidomide compared with melphalan was £46,000 per QALY gained. The ERG's analysis, which included a shorter tail for the progression-free survival curve for the comparator, gave an ICER of £48,000 per QALY gained. The committee concluded that the most plausible ICER lay above either £46,000 or £48,000 per QALY gained because melphalan was likely to be more effective than dexamethasone (see section 4.12).

4.21   The committee explored alternative scenarios and was aware that several analyses gave ICERs between £20,000 and £30,000 per QALY gained:

- The company's analysis using progression-free survival data from Petrucci et al. after which the effectiveness of melphalan was assumed to be the same as the lenalidomide arm of the model, gave an ICER of £22,172 per QALY gained.

- Two analyses presented by the company assumed that melphalan had the same clinical effectiveness as dexamethasone until the point of disease progression, after which the effectiveness of melphalan was informed by Petrucci et al. These analyses resulted in ICERs of about £24,000 per QALY gained.

The committee agreed that using comparator data from Petrucci et al. had several fundamental problems and was not suitable for decision-making (see section 4.9). It further agreed that these limitations applied whether the Petrucci et al. data were used for the entire course of the disease or only part of it. The committee concluded that none of these analyses were plausible.

Innovation

4.22   The committee discussed whether lenalidomide is innovative in that it is a step change in treatment and offers a significant and substantial impact on health-related benefits not captured by the modelling. It did not consider lenalidomide a step change because it was already offered to patients with myeloma at a later stage of the disease. The committee agreed that, as an oral treatment, lenalidomide would be convenient, and could save time and resources for people with multiple myeloma. It thought that this benefit may not have been captured in the calculation of the QALYs. The committee concluded that it was unclear how this could be modelled, and that it was unlikely to make a substantial difference to its conclusions given the high ICERs.

Cancer Drugs Fund

4.23   The committee discussed the new arrangements for the Cancer Drugs Fund recently agreed by NICE and NHS England, noting the [addendum to the NICE process and methods guides](). The committee agreed that it had not been presented with a plausible ICER that was below the range normally considered a cost effective use of NHS resources (see sections 4.20 and 4.21). So, the committee agreed that lenalidomide did

not have the plausible potential to be cost effective at its current price. It also considered that, although there were uncertainties in the comparative effectiveness evidence for this appraisal, the clinical-effectiveness evidence from MM-009 and MM-010 for lenalidomide was relatively mature and it was not aware of any ongoing studies that could reduce this clinical uncertainty. Furthermore, the committee considered that collecting observational data from people having lenalidomide in the NHS would not address the clinical uncertainties, and would not substantially inform a subsequent update of the guidance. The committee concluded that lenalidomide did not meet the criteria to be considered for use within the Cancer Drugs Fund.

End-of-life considerations

4.24 The committee considered supplementary advice from NICE that should be taken into account when appraising treatments that may extend the life of patients with a short life expectancy. For this advice to be applied, all the following criteria must be met:

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

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

4.25 The committee considered whether lenalidomide meets the end-of-life criteria for people with multiple myeloma who have had 1 prior treatment with bortezomib, and for whom thalidomide treatment and stem cell transplantation are not suitable. It was aware that the company had not presented data to support considering lenalidomide as an end-of-life

therapy. It noted that the model predicted that patients in the comparator arms lived longer than 24 months, and therefore concluded that lenalidomide in this appraisal did not meet the criterion for life expectancy. The committee agreed that it did not need to discuss the remaining criterion.

Pharmaceutical Price Regulation Scheme 2014

4.26   The committee was aware of NICE's position statement on the Pharmaceutical Price Regulation Scheme (PPRS) 2014, and in particular the PPRS payment mechanism. It accepted the conclusion 'that the 2014 PPRS payment mechanism should not, as a matter of course, be regarded as a relevant consideration in its assessment of the cost effectiveness of branded medicines'. The committee heard nothing to support taking a different view about the relevance of the PPRS to this appraisal. It concluded that the PPRS payment mechanism was not relevant in considering the cost effectiveness of the technology in this appraisal.

Conclusion

4.27   The committee concluded that the most plausible ICER for lenalidomide compared with melphalan was likely to exceed £46,000 or £48,000 per QALY gained, which was substantially above the range of a cost-effective treatment. Therefore, the committee could not recommend lenalidomide as a cost-effective use of NHS resources.

Summary of appraisal committee's key conclusions

TAXXX	Appraisal title: Lenalidomide for treating multiple myeloma after 1 prior treatment with bortezomib	Section
Key conclusion		

Lenalidomide in combination with dexamethasone is not recommended for treating multiple myeloma in adults: • whose condition has relapsed for the first time • who have had 1 prior treatment with bortezomib • when thalidomide is contraindicated or not suitable and • when stem cell transplantation is not suitable.	1.1
The committee concluded that lenalidomide was likely to be more effective than melphalan (cytotoxic chemotherapy). A crude indirect comparison suggested that median survival times were substantially longer for patients having lenalidomide plus dexamethasone compared with melphalan. The data for melphalan was taken from a small single-arm trial and was at high risk of bias. However, the data favoured lenalidomide with a large benefit, and this was supported by clinical expert opinion.	4.6
The committee concluded that the most plausible incremental cost-effectiveness ratio (ICER) for lenalidomide compared with melphalan lay above either £46,000 or £48,000 per quality-adjusted life year (QALY) gained because melphalan was likely to be more effective than dexamethasone.	4.20

Current practice		
Clinical need of patients, including the availability of alternative treatments	The committee heard how important it was for people who are unable to have thalidomide first line to have options for treatment after first relapse with bortezomib.	4.1 to 4.3
The technology		

Proposed benefits of the technology How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?	The committee agreed that, as an oral treatment, lenalidomide would be convenient and could save time and resources.	4.1
What is the position of the treatment in the pathway of care for the condition?	Lenalidomide in combination with dexamethasone has a marketing authorisation for treating 'multiple myeloma in adult patients who have received at least one prior therapy'.	2
Adverse reactions	The summary of product characteristics includes the following adverse effects for lenalidomide: neutropenia, anaemia and thrombocytopenia. Because lenalidomide is structurally related to thalidomide, a known human teratogen that causes severe birth defects, a risk minimisation plan has been developed and agreed with the Medicines and Healthcare products Regulatory Agency to avoid fetal exposure to lenalidomide.	2
Evidence for clinical effectiveness		
Availability, nature and quality of evidence	The company presented evidence from 2 randomised clinical trials, MM-009 and MM-010, to show the effectiveness of lenalidomide. However, the trials compared lenalidomide plus dexamethasone with	4.3 to 4.5

	placebo plus dexamethasone. Although dexamethasone alone was not a comparator in the decision problem, data from both arms of the trials were used to inform the health economic model.	4.14
	The committee noted there were no trials comparing lenalidomide with cytotoxic chemotherapy, and that the company estimated the clinical effectiveness of cytotoxic chemotherapy using data from a small single-arm trial without a control group. The company used a crude indirect comparison with the lenalidomide arm in MM-009 and MM-010. The committee was aware that this non-randomised comparison was at high risk of bias, and agreed that the evidence was very uncertain. Accordingly, for economic modelling, the committee preferred to use data from the comparator arm of the MM-009 and MM-010 trials (dexamethasone monotherapy) to model the effectiveness of melphalan.	4.6 4.14
Relevance to general clinical practice in the NHS	The committee recognised that the population in MM-009 and MM-010 did not match the population set out in the decision problem for this appraisal. However, the committee heard from the clinical expert that, based on their experience, the results from MM-009 and MM-010 were generalisable to the population of interest.	4.5

Uncertainties generated by the evidence	There was uncertainty in the relative effectiveness (progression-free and overall survival) of lenalidomide compared with melphalan. The company calculated a crude hazard ratio by taking the ratio of median survival times with melphalan compared with lenalidomide. The committee agreed that there was significant uncertainty associated with this crude indirect comparison using non-randomised evidence from a small single-arm trial.	4.6, 4.10
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	No clinically relevant subgroups were identified.	-
Estimate of the size of the clinical effectiveness including strength of supporting evidence	The committee concluded that, although there was significant uncertainty in the evidence, lenalidomide was likely to be more effective than cytotoxic chemotherapy for treating multiple myeloma in the population relevant to this appraisal.	4.6

| How has the new clinical evidence that has emerged since the original appraisal (TA171) influenced the current recommendations? | The same clinical trials as in NICE's technology appraisal guidance on [lenalidomide for the treatment of multiple myeloma in people who have received at least one prior therapy](#) (MM-009 and MM-010) were presented to show the effectiveness of lenalidomide plus dexamethasone and placebo plus dexamethasone. The evidence presented in this appraisal included an extended follow-up of overall survival, which was not included in technology appraisal (TA) 171. This added further support to the evidence that lenalidomide was clinically effective compared with placebo. | 4.4, 4.5 |
| **Evidence for cost effectiveness** | | |

| Availability and nature of evidence | The company's multistate model compared lenalidomide plus dexamethasone with chemotherapy. The company used 'multistate' modelling because it meant that the survival curves for progression-free and overall survival did not cross (this had been a problem in previous versions of the model). | 4.7 |
| | The committee considered 2 main approaches to the modelling based on:

• a crude indirect comparison
• assuming that melphalan had the same clinical effectiveness as dexamethasone.

The committee preferred the second approach. | 4.9, 4.14 |

Uncertainties around and plausibility of assumptions and inputs in the economic model	The committee agreed that there were 4 fundamental problems with the company's model based on a crude indirect comparison: • it was at high risk of bias • the melphalan data came from only 34 patients • the statistical techniques may not have been technically correct • the model predictions lacked external validity. The committee concluded that this model was not suitable for decision-making.	4.9
	The company, evidence review group and committee agreed that the analyses assuming equivalence of melphalan to dexamethasone offered several advantages over using a crude indirect comparison. This approach used randomised data so was at low risk of bias and accurately captured the impact of third-line lenalidomide. However, it agreed this analysis may have underestimated the ICER for lenalidomide compared with melphalan because clinical advice suggests that melphalan might be more effective than dexamethasone. The committee concluded that the analysis assuming equivalence was preferable to the approach based on a crude indirect comparison.	4.14, 4.15

Incorporation of health-related quality-of-life benefits and utility values Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?	Although the committee had some concerns about the utility values used in the modelling, this was not a key driver of the decision. The benefit of oral treatment was not included in the analysis. However, the committee concluded that it was unclear how this could be modelled, and that it was unlikely to make a substantive difference to its conclusions considering the high level of uncertainty.	4.19 4.22
Are there specific groups of people for whom the technology is particularly cost effective?	No relevant subgroups were identified.	-
What are the key drivers of cost effectiveness?	The key driver of cost effectiveness was the choice of whether to base the model on: • a crude indirect comparison with melphalan • the randomised trial data from MM-009 and MM-010, assuming melphalan was equivalent to dexamethasone The committee preferred the second approach.	4.7, 4.14

Most likely cost-effectiveness estimate (given as an ICER)	The committee concluded that the most plausible ICER for lenalidomide compared with melphalan lay above either £46,000 or £48,000 per QALY gained. The committee agreed the ICER was likely to be above these values because melphalan was likely to be more effective than dexamethasone but this benefit was not included in the model. It therefore concluded that lenalidomide could not be recommended as a cost-effective use of NHS resources for people with multiple myeloma for whom thalidomide treatment and stem cell transplant were not suitable, and who had received 1 prior treatment with bortezomib.	4.20, 4.27
How has the new cost-effectiveness evidence that has emerged since the original appraisal (TA171) influenced the current recommendations?	The company identified no new health economic studies from the literature, but presented several iterations of a new multi-state model.

The preliminary recommendations for lenalidomide for treating multiple myeloma after first relapse have not changed from TA171. | 4.7

1.1 |
| **Additional factors taken into account** | | |
| Patient access schemes (PPRS) | The company proposed a complex patient access scheme. This was included in the modelling. | 2 |

End-of-life considerations	The company had not presented data to support lenalidomide as an end-of-life therapy. The committee noted that the number of life years estimated in the comparator arm of the model was greater than 24 months, and therefore concluded that the end-of-life criteria had not been met.	4.24
Equalities considerations and social value judgements	Not applicable.	-

5   Proposed date for review of guidance

5.1   NICE proposes that the guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Dr Amanda Adler
Chair, appraisal committee
November 2016

6   Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee B.

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.

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.

Carl Prescott
Technical Lead

Abitha Senthinathan
Technical Lead

Rosie Lovett
Technical Adviser

Melinda Goodall
Technical Adviser

Jeremy Powell
Project Manager

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