

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Lenalidomide maintenance treatment after an autologous stem cell transplant for newly diagnosed multiple myeloma

The Department of Health and Social Care 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 document.
- Subject to any appeal by consultees, the final appraisal document 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: 29 September 2020

Second appraisal committee meeting: TBC

Details of membership of the appraisal committee are given in section 5

1 Recommendations

- 1.1 Lenalidomide is not recommended, within its marketing authorisation, as maintenance treatment after an autologous stem cell transplant for newly diagnosed multiple myeloma in adults.
- 1.2 This recommendation is not intended to affect treatment with lenalidomide that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

Why the committee made these recommendations

There is currently no maintenance treatment for newly diagnosed multiple myeloma in people who have had an autologous stem cell transplant. The condition is usually monitored until it gets worse.

Clinical trial results show that, compared with monitoring alone, lenalidomide increases how long people live and extends the time before the condition gets worse.

The cost-effectiveness estimates are uncertain. This is because of limitations in the cost-effectiveness model, and because the model might not reflect what happens in the NHS in England. Therefore, lenalidomide is not recommended for use in the NHS for this indication.

2 Information about lenalidomide

Marketing authorisation indication

- 2.1 Lenalidomide (Revlimid, Celgene) is indicated for 'the maintenance treatment of adult patients with newly diagnosed multiple myeloma who have undergone autologous stem cell transplantation'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the [summary of product characteristics](#).

Price

2.3 The list price for lenalidomide is £3,780 per pack of 21 tablets, each containing 10 mg of the active ingredient (excluding VAT; BNF online, August 2020). The company has a commercial arrangement. This makes lenalidomide available to the NHS with a discount, which would have applied to this indication if the technology had been recommended. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

3 Committee discussion

The appraisal committee (section 5) considered evidence submitted by Celgene, a review of this submission by the evidence review group (ERG), NICE's technical report and responses from stakeholders. See the [committee papers](#) for full details of the evidence.

Treatment pathway

Lenalidomide is the only potential option for maintenance treatment for multiple myeloma after an autologous stem cell transplant

3.1 After a first autologous stem cell transplant, newly diagnosed multiple myeloma is usually monitored until the first relapse, and not actively treated. Lenalidomide is the only treatment option licensed as a maintenance therapy to replace monitoring for this indication. Lenalidomide would be used to try to prolong the time until first relapse. The clinical experts advised that most people with newly diagnosed multiple myeloma who have had a first transplant would have lenalidomide maintenance treatment if it was recommended, and that only

a small proportion would have no active treatment. The committee was aware that lenalidomide (plus dexamethasone) is currently available in the NHS for treating multiple myeloma later in the treatment pathway. The clinical experts explained that if people had lenalidomide maintenance treatment they would not then have lenalidomide again later in the treatment pathway. However, the clinical and patient experts emphasised that the benefits of lenalidomide maintenance treatment outweigh the benefits of using it later in the pathway. This is because, with each line of new therapy, a substantial proportion of people stop having treatment because they become too ill or have complications. Therefore, the most effective treatments should be given as soon as possible. Also, the first remission is often the 'best' remission because it is when people with the condition are at their fittest. It is also when they have the highest quality of life, before the negative effect of the disease and its treatments have accumulated. Therefore, extending the first remission maximises the chances of people maintaining a higher quality of life for the longest possible period. The patient experts also explained that lenalidomide is a well-tolerated treatment and that, during the ongoing COVID-19 pandemic, it is particularly convenient. This is because it is taken orally and does not need a hospital visit. The committee concluded that, if recommended, lenalidomide would replace monitoring for most people with newly diagnosed multiple myeloma who have had an autologous stem cell transplant.

The number of people having a second autologous stem cell transplant is decreasing as alternative treatment options become available

- 3.2 The committee discussed whether a second autologous stem cell transplant may be an option for some people after a first relapse after their first transplant. The company explained that second transplants would be highly unlikely in clinical practice, while the ERG stated that they are a relevant option. The clinical experts advised that about 5% to 10% of people get a second transplant. Most of these people have had a very long remission after their first transplant and are fit enough to have a

second transplant. The clinical and patient experts agreed that the availability of effective treatments in the Cancer Drugs Fund has led to decreasing rates of second transplants. They thought that these rates would decrease more if lenalidomide maintenance treatment was recommended. The committee concluded that about 5% to 10% of people currently get a second autologous stem cell transplant, but these numbers are likely to fall in the future as alternative treatment options become available.

Licensed dose

The dosing schedule that would be used in clinical practice is different to that in the marketing authorisation

3.3 The lenalidomide marketing authorisation recommends a dosage of 10 mg once daily on days 1 to 28 of repeated 28-day cycles. However, the dosage in the company's submission is 10 mg once daily on days 1 to 21 of repeated 28-day cycles. This was also the dosing schedule used in Myeloma XI, which was the main source of clinical evidence in the company's submission. The company stated that 21 days of dosing followed by a 7-day break would be used in the NHS. This is because it is used for all other lenalidomide indications and is the dosage that healthcare professionals are familiar with. The company highlighted that there may be safety and tolerability benefits associated with having a treatment-free week. It added that this might mean that people would stay on lenalidomide treatment for longer overall with the 21-day schedule compared with the 28-day schedule. It claimed that using a lenalidomide dosage that is tolerated for as long as possible would fit with the aim of maintenance treatment, which is to avoid relapse for as long as possible. The company explained that the only reason the licence specifies a 28-day dosing schedule is because the marketing authorisation was based on the CALGB 100104 and IFM 2005-02 trials, both of which used a 28-day dosing schedule. The company also explained that, despite dose increases from 10 mg to 15 mg allowed in the licence, this would be

unlikely in clinical practice. This is because the risk of safety and tolerability issues would be higher with the 15 mg dose. The committee heard unanimous support for, and agreement with, all of the company's views on the dosing schedule from the ERG, the patient and clinical experts, and other stakeholders. The committee concluded that a 21-day dosing schedule would likely be used in clinical practice, but it noted this is off label. It also concluded that it would need to consider clinical- and cost-effectiveness data for the 28-day dosing schedule because it reflects the marketing authorisation.

Clinical evidence

Lenalidomide is an effective maintenance treatment for people who have had an autologous stem cell transplant

3.4 The main clinical evidence for lenalidomide maintenance treatment came from Myeloma XI, a phase 3 open-label randomised trial based in 110 NHS centres in the UK. A total of 1,971 people with newly diagnosed multiple myeloma were enrolled and stratified by their eligibility for an autologous stem cell transplant. The trial had an adaptive design in which ongoing trial results were used to inform changes in the protocol. Also, there were multiple levels of randomisation in the trial. The company's submission focused on a smaller cohort of 1,032 people from Myeloma XI. These people had had a first transplant and been randomised to have maintenance with lenalidomide 10 mg daily on days 1 to 21 of each 28-day cycle, or to have monitoring of their disease with no lenalidomide treatment. The company considered this cohort to be directly relevant to this appraisal (when Myeloma XI is mentioned from this point, it is referring to this cohort of interest unless otherwise specified). The primary outcomes were progression-free survival and overall survival, both of which were statistically significantly longer with lenalidomide maintenance treatment than with monitoring. The clinical experts advised that the trial was representative of NHS practice, and that the results were generalisable to the population in this appraisal. Based on the results from

Myeloma XI, the committee concluded that lenalidomide is an effective maintenance treatment for newly diagnosed multiple myeloma in people who have had an autologous stem cell transplant.

The company should have presented evidence from other trials of lenalidomide maintenance treatment

3.5 The company identified 4 studies of lenalidomide maintenance treatment in its systematic literature review: Myeloma XI, CALGB 100104, GIMEMA and IFM 2005-02. It then applied a subsequent set of criteria to exclude CALGB 100104, GIMEMA, and IFM 2005-02, leaving only Myeloma XI as a source of clinical-effectiveness evidence. The company argued that Myeloma XI was the only trial that reflected the decision problem and UK clinical practice. However, it used both CALGB 100104 and Myeloma XI data for survival estimates in its cost-effectiveness model. The ERG thought that this meant the company's approach was inconsistent. The ERG was also concerned that the subsequent set of criteria used to exclude trials was arbitrary and not prespecified. It considered that IFM 2005-02 should have been excluded based on the company's original systematic literature review criteria, but that CALGB 100104 and GIMEMA should have been included. The committee agreed that the company's approach was inconsistent and would have preferred the company to present all trials meeting the original systematic literature review criteria. The committee also acknowledged that the cohort of interest from Myeloma XI was likely to provide the most generalisable source of clinical-effectiveness evidence to NHS practice. However, because the marketing authorisation is based on trials with 28-days of dosing, the committee stated that it needed to see more evidence on the clinical effectiveness at this dosage.

The safety profile of lenalidomide as a maintenance treatment compared with monitoring alone is likely to be acceptable

3.6 The company explained that there were no adverse-events data available from Myeloma XI for the monitoring arm of the cohort of interest. The ERG

stated that this was an area of uncertainty because between-arm comparisons of adverse event rates were needed to understand the comparative safety profile of lenalidomide maintenance treatment. The company provided adverse-events data from both the lenalidomide and monitoring arms of CALGB 100104. The ERG thought that it was useful as supplementary information but that it was not directly generalisable to the population in the NHS. The clinical experts considered that the rates of adverse events in the lenalidomide arm of Myeloma XI for the cohort of interest were similar to those seen in clinical practice for other indications. A patient expert explained that results from a survey done by Myeloma UK showed that most people having lenalidomide maintenance treatment found it easy to take and tolerated it well. The committee acknowledged that there was some uncertainty about the risk of adverse events with lenalidomide maintenance treatment compared with monitoring. However, it concluded that the safety profile was likely to be acceptable.

The company's economic model

The company's model structure does not allow assumptions about subsequent treatments to be explored

- 3.7 The company chose a partitioned survival model comprising 3 health states (pre-progression, progressive disease and death). It explained that it had previously considered a more complex model structure such as a multistate model. However, there were insufficient data to estimate transition probabilities for this approach, so it chose a partitioned survival model instead. The ERG stated that the simple structure of the company's model did not allow uncertainty in the model to be fully explored. It was particularly concerned about the effect of subsequent treatments. This was because survival in the company's model was based on Myeloma XI and CALGB 100104, and the treatments given at second line and beyond in these trials are not generalisable to current NHS practice. The treatment of myeloma has changed since Myeloma XI was started, which

means that, despite it being a UK trial, the treatments used do not reflect current NHS practice. Also, CALGB 100104 has limited generalisability to the UK because it was based in the US. The ERG highlighted that the company's partitioned survival model structure did not allow alternative assumptions about subsequent treatments to be explored. This meant that the modelled survival may not have been representative of what would be seen in the NHS. The committee concluded that the company's model structure had limitations. It also concluded that there was likely to be uncertainty around the cost-effectiveness estimate because assumptions about the effects of subsequent therapies on survival could not be fully explored.

The company's methods and rationale for pooling Myeloma XI and CALGB 100104 data, and adjusting for treatment switching, are unclear

3.8 Survival models were needed to predict survival beyond the end of the clinical trials for lenalidomide maintenance treatment. In its original base case, the company fitted survival curves to Myeloma XI data and used CALGB 100104 data to help with curve selection. However, in response to technical engagement, it pooled data from Myeloma XI and CALGB 100104, and fitted curves to the pooled data. It confirmed that it used a simple method for pooling the individual patient data from the trials. This did not involve adjusting CALGB 100104 data to reflect Myeloma XI, for example by adjusting for differences in trial design or population. The ERG noted that it was unable to validate the company's methods for pooling data because insufficient detail was provided. The committee noted that the pooling of Myeloma XI and CALGB 100104 data was essentially a meta-analysis. It was disappointed that the company's approach could not be scrutinised and validated based on the information provided. The committee suggested that the company should have justified its choice to pool data and to use a simple pooling approach over other evidence synthesis methods. Also, the company may have been able to explore the assumption that both Myeloma XI and CALGB 100104 were estimating the same underlying treatment effect, and therefore were

suitable for evidence synthesis. It could have done this by fitting an interaction term between the fixed effect on treatment and study. However, it did not appear to have explored this. The company explained that it used the rank-preserving structural-failure time method to adjust for treatment switching in CALGB 100104 and that it did not explore any alternative approaches. The committee recognised that different treatment-switching adjustment methods were available and was disappointed the company did not provide any justification for using its chosen method. It concluded that the company's methods and rationale for pooling Myeloma XI and CALGB 100104 data, and adjusting for treatment switching, were unclear.

Survival extrapolations should use Myeloma XI data as the main source of evidence but could be supplemented with CALGB 100104 data

3.9 The company and ERG had different preferred approaches to using trial data for survival extrapolations. The company preferred to use data from both Myeloma XI and CALGB 100104 because CALGB 100104 provided longer-term data. It also mentioned that, despite heterogeneity between the trials, the survival results were very similar. The ERG preferred to use Myeloma XI data only because of key differences between the 2 trials, such as dosing, baseline characteristics and subsequent treatments. The committee acknowledged that the differences between the trials meant a simple pooling approach may have been inappropriate (see [section 3.8](#)). In particular, the 28-day dosing regimen in CALGB 100104 meant survival in the model was based on a dosage that the company, ERG, and patient and clinical experts explained would not be given in NHS practice. As such, the company's survival estimates may have been optimistic because people were assumed to be benefiting from an extra 7 days of dosing. The committee recognised that CALGB 100104 had a longer median follow up (91 months) than Myeloma XI (31 months), so might have provided some useful information about longer-term survival. The committee concluded that it would prefer to see a survival analysis that used Myeloma XI as the main source of evidence. CALGB 100104 could

be used to help extrapolation, with data adjusted to reflect the Myeloma XI population as far as possible and conditional on the underlying survival of patients in Myeloma XI.

Waning of treatment effect

The treatment effect of lenalidomide maintenance may wane over time and this should be included in the model

3.10 Treatment waning refers to whether or not the relative treatment effect between lenalidomide and monitoring of the condition is likely to reduce over time after people stop taking lenalidomide. Not including treatment waning in the model implies that the relative treatment effect stays the same and lenalidomide remains more effective than monitoring for the entire modelled time horizon, even if people are no longer on treatment. Based on its survival curves, the company took the view that there was no evidence of a treatment-waning effect with lenalidomide. The ERG did not include a treatment-waning effect in its base case but explained that there were no long-term data to rule out the possibility that the relative treatment effect decreases over time. The ERG therefore did a scenario analysis that looked at different treatment-waning scenarios. It found the cost-effectiveness estimate to be sensitive to assumptions about how long the treatment effect lasts for. The clinical experts advised that they would not expect lenalidomide to have a continued effect after people had stopped taking it. The committee would therefore like to see an analysis in which the relative treatment effect for lenalidomide diminished over time beyond the end of the trial period, which reflects clinically plausible scenarios. The committee concluded that the treatment effect of lenalidomide therapy may wane over time and that this should have been included in the company's model.

Costs of subsequent treatments

Costs of subsequent treatments are highly uncertain so scenarios should be presented

3.11 The company's model included the costs of second- and third-line treatments given after maintenance treatment. The committee was aware that the subsequent therapies used in Myeloma XI are no longer generalisable to NHS practice. The clinical experts explained that most people who have had a first autologous stem cell transplant will go on to have a treatment recommended in the Cancer Drugs Fund at a later line of therapy. However, the [NICE Cancer Drugs Fund position statement](#) specifies that companies should not include treatments recommended for use in the Cancer Drugs Fund as treatment-sequence products in their economic modelling. This is because they do not yet reflect routine NHS practice. The committee acknowledged that this made it difficult to develop assumptions about subsequent therapies in the model, and that any assumptions were hypothetical and highly uncertain. The company developed a set of assumptions about the proportions of different therapies used at second and third line in the model. The ERG highlighted some concerns about these assumptions. It disagreed that there would be differences in the proportion of people with 'no treatment' at third line between arms. Also, it did not think lenalidomide or carfilzomib should be used second line because neither is currently recommended by NICE at this position in the pathway. The ERG therefore developed its own set of assumptions. The Cancer Drugs Fund clinical lead estimated that, if treatments recommended for use in the Cancer Drugs Fund were not available, about half of people whose condition was monitored after their first transplant would then have lenalidomide plus dexamethasone after their first relapse. The clinical experts agreed with this estimate. The committee recognised the company's and ERG's attempts to explore different subsequent therapy assumptions. It was satisfied that the rates of second transplants would be 5% to 10% (see [section 3.2](#)), but that the

other assumptions could not be verified so should be explored in more detail. The committee concluded that it would have liked to see a range of scenarios because of the high levels of uncertainty. It also concluded that these assumptions should have reflected as closely as possible treatments that are currently given in NHS practice, and what would be given in the absence of Cancer Drugs Fund treatments.

Dose adjustments and drug wastage

Myeloma XI trial data should be used to estimate relative dose intensity

3.12 Relative dose intensity is the percentage of the prescribed dose of lenalidomide that people take. Assumptions about the relative dose intensity could affect the cost-effectiveness estimate because it shows how much of the total cost of a prescribed drug is incurred (with a lower relative dose intensity meaning lower accrued drug costs). The company used individual patient data from Myeloma XI to estimate the relative dose intensity for lenalidomide maintenance treatment. This is commercial in confidence so cannot be stated here. The ERG's opinion was that the company's relative dose-intensity estimate was too low, so the cost-effectiveness estimate was optimistic. It noted that the company's relative dose-intensity estimate from Myeloma XI was lower than in TOURMALINE-MM1 (TMM1). This trial was found by the ERG and was in people with relapsed or refractory multiple myeloma so was not directly relevant to this appraisal. TMM1 had used a higher lenalidomide dose of 25 mg daily on days 1 to 21 of each 28-day cycle. The ERG argued that this was counterintuitive because people taking a higher dose would be expected to have more safety and tolerability issues, so would be less likely to maintain the target dose. It therefore used the relative dose intensity of 94.9% from TMM1 in its own base case. The ERG also considered that the company did not provide enough clear information to allow for its relative dose-intensity calculation to be validated. The committee was aware of the higher relative dose-intensity estimate from TMM1 compared with Myeloma XI. However, it decided that Myeloma XI

was a better source of information because it was directly relevant to the decision problem and was based in the UK. Conversely, TMM1 included people with relapsed and refractory multiple myeloma and was international. The committee concluded that Myeloma XI should have been used to estimate relative dose intensity. It also concluded that the company should have provided the full methods it used to determine this so that the ERG could validate it.

Cost-effectiveness estimate

No analyses reflect the committee's preferred assumptions

3.13 Because of confidential commercial arrangements for lenalidomide and other treatments in the model, the cost-effectiveness results cannot be reported here. However, none of the company's nor the ERG's analyses reflected the committee's preferences. The committee would have preferred to see:

- clinical-effectiveness evidence from the CALGB-100104 and GIMEMA trials of lenalidomide maintenance treatment (see [section 3.5](#))
- survival estimates in the economic model based on Myeloma XI data, with CALGB 100104 data (adjusted to reflect the Myeloma XI population as closely as possible, and conditional on the underlying survival of patients in Myeloma XI) used to help longer-term extrapolation, with all methods explained in detail (see [section 3.9](#))
- the company's justification for using the rank-preserving structural-failure time model over other methods to adjust for treatment switching in CALGB 100104 (see [section 3.8](#))
- waning of the treatment effect of lenalidomide (see [section 3.10](#))
- 5% to 10% of people having a second autologous stem cell transplant, and a range of assumptions for the proportions of people having other subsequent therapies for the purposes of estimating subsequent treatment costs in the model (see [section 3.11](#))

- detailed methods for how the relative dose intensity was calculated using Myeloma XI data (see [section 3.12](#))
- a model scenario reflecting a 1-day to 28-day lenalidomide treatment regimen (see [section 3.3](#)).

Other factors

There is no evidence to suggest any additional benefits not adequately captured by the quality-adjusted life years and no equalities issues

3.14 The committee was aware that there is currently no active maintenance treatment for newly diagnosed multiple myeloma in adults who have had an autologous stem cell transplant in the UK, which represents a gap in NHS practice. However, it saw no evidence to suggest additional benefits not adequately captured by the quality-adjusted life years. No equality or social value judgement issues were identified.

Conclusion

Lenalidomide maintenance treatment is not recommended for routine use in the NHS

3.15 The clinical trial results showed that lenalidomide maintenance treatment improves survival and extends the time before first relapse compared with monitoring alone in people with newly diagnosed multiple myeloma who have had an autologous stem cell transplant. However, the costs and effects of subsequent treatments in the lenalidomide clinical trials did not reflect NHS clinical practice in England. Also, the cost-effectiveness estimates were uncertain because the company did not present some of its methods in enough detail to be adequately scrutinised. In addition, none of the company's analyses reflected the committee's preferred assumptions. Therefore, the committee did not recommend lenalidomide maintenance treatment for routine use in the NHS for newly diagnosed multiple myeloma in adults who have had an autologous stem cell transplant.

4 Proposed date for review of guidance

- 4.1 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.

Sanjeev Patel

Chair, appraisal committee

August 2020

5 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.

Hannah Nicholas

Technical lead

Carl Prescott

Technical adviser

Eleanor Donegan

Technical adviser

Jeremy Powell

Project manager

ISBN: [to be added at publication]