

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final appraisal document

Lenalidomide plus dexamethasone for previously untreated multiple myeloma

1 Recommendations

- 1.1 Lenalidomide plus dexamethasone is recommended as an option for previously untreated multiple myeloma in adults who are not eligible for a stem cell transplant, only if:
- thalidomide is contraindicated (including for pre-existing conditions that it may aggravate) or
 - the person cannot tolerate thalidomide, and
 - the company provides lenalidomide according to the commercial arrangement.
- 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

Previously untreated multiple myeloma is normally treated with thalidomide-based therapy. If people cannot take thalidomide, bortezomib-based therapy is used. There is a high unmet need for new treatment options for people who cannot take thalidomide, so that they can have newer treatments later.

Evidence from an indirect comparison suggests that lenalidomide plus dexamethasone substantially improves the length of time people live compared with bortezomib-based therapy.

The most plausible cost-effectiveness estimate for lenalidomide plus dexamethasone for people unable to take thalidomide is within the range that NICE normally considers a cost-effective use of NHS resources. Because of this and the high unmet need, lenalidomide plus dexamethasone can be recommended for people unable to take thalidomide.

Lenalidomide plus dexamethasone cannot be recommended for untreated multiple myeloma in people who could take thalidomide because this would not be cost effective. Because the definition of thalidomide intolerance in clinical practice varies, it is appropriate that NHS England clearly defines who would be eligible for treatment with lenalidomide plus dexamethasone (see section 3.2).

2 Information about lenalidomide

Marketing authorisation indication	Lenalidomide (Revlimid, Celgene) as combination therapy is indicated for 'the treatment of adult patients with previously untreated multiple myeloma who are not eligible for transplant'.
Dosage in the marketing authorisation	The recommended starting dosage is 25 mg orally once daily on days 1 to 21 of repeated 28-day cycles.
Price	<p>Lenalidomide is available as a 21-capsule pack. The cost per pack (excluding VAT; British National Formulary online, accessed April 2019) varies according to capsule size: £3,426.00 (2.5 mg), £3,570.00 (5 mg), £3,675.00 (7.5 mg), £3,780.00 (10 mg), £3,969.00 (15 mg), £4,168.50 (20 mg) and £4,368.00 (25 mg).</p> <p>The company has a commercial arrangement (simple discount patient access scheme). This makes lenalidomide available to the NHS with a discount. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.</p>

3 Committee discussion

The appraisal committee (section 6) considered evidence submitted by Celgene and a review of this submission by the evidence review group (ERG). See the [committee papers](#) for full details of the evidence.

Current treatments

There is an unmet need for new effective treatments, especially for people unable to take thalidomide

- 3.1 Treatment for untreated multiple myeloma is either a thalidomide-based therapy or, if a person is unable to take thalidomide, a bortezomib-based therapy. Both thalidomide and bortezomib are combined with an alkylating agent and a corticosteroid. The clinical experts explained that the current treatment options can be difficult to tolerate because the combination of 3 drugs can cause substantial side effects. After disease progression, people are offered treatment depending on their initial therapy. People who have had first-line thalidomide-based therapy can have either second-line bortezomib- or carfilzomib-based therapy. People who cannot

take thalidomide have first-line bortezomib-based therapy followed by second-line cytotoxic chemotherapy. After subsequent disease progression, people can have newer therapy options, including third-line lenalidomide- or panobinostat-based therapies and fourth-line pomalidomide-based therapy. The patient and clinical experts explained that cytotoxic chemotherapy is considered to be less effective than the newer therapy options. Therefore, there is an unmet need for new treatments for untreated multiple myeloma to allow people who cannot take thalidomide to have second-line bortezomib- or carfilzomib-based therapy after first progression, thereby avoiding cytotoxic chemotherapy. The committee recognised that lenalidomide plus dexamethasone, as a first-line treatment, would fulfil an unmet need for all patients, especially for those who cannot have thalidomide.

It is unclear who cannot take thalidomide in clinical practice

3.2 The Cancer Drugs Fund clinical lead explained that it is unclear who cannot take thalidomide in clinical practice. The committee was aware that NICE's guidance for [bortezomib and thalidomide for the first-line treatment of multiple myeloma](#) did not define the people who cannot have thalidomide. The Cancer Drugs Fund clinical lead explained that this has led to a much wider group having bortezomib than those who cannot have thalidomide because of true contraindications or intolerance. Specifically, at least 50% of people with newly diagnosed myeloma who are not eligible for a stem cell transplant are currently having first-line bortezomib-based therapy, about 25% are having thalidomide-based therapy and about 25% are having cytotoxic chemotherapy. The clinical experts agreed that there are no standard criteria to define who cannot have thalidomide-based treatment in clinical practice, but these might include people who:

- could not tolerate a 3-drug therapy
- have pre-existing neuropathy
- need to use opiates because of bone involvement of myeloma

- have somnolence (sleepiness or drowsiness).

The committee recognised that these groups may include a high proportion of older people. It concluded that people for whom thalidomide is unsuitable can be in 1 of 2 groups:

- people who cannot have thalidomide from the outset because it is contraindicated (as listed in the thalidomide summary of product characteristics), or because they have a pre-existing condition that thalidomide may aggravate (most importantly, peripheral neuropathy)
- people for whom a planned course of thalidomide causes unacceptable toxicity that outweighs the benefit of continued therapy.

The committee agreed that it could not define this population any further because there are no strict criteria used in clinical practice to determine who can or cannot take thalidomide. However, it expected that clinicians would exercise their judgement when deciding whether someone can take thalidomide, taking into account the contraindications in the summary of product characteristics, the person's medical history and pre-existing conditions, and the effect of toxicity on overall treatment benefit. To help clinicians do this, it would be beneficial to have clear guidance from the commissioner, NHS England.

Company's decision problem

The choice of comparators is suitable for decision making

- 3.3 The company's submission compared lenalidomide plus dexamethasone with thalidomide plus melphalan plus prednisone (MPT) for the population who can have thalidomide. For people unable to tolerate thalidomide or for whom it is contraindicated, the company compared lenalidomide plus dexamethasone with bortezomib (Velcade) plus melphalan plus prednisone (VMP). The clinical experts commented that, in clinical practice in England, the alkylating agent cyclophosphamide is more often

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used as part of thalidomide- or bortezomib-based therapy than melphalan. However, they explained that cyclophosphamide and melphalan are clinically equivalent, and have similar costs. The committee concluded that the comparators chosen by the company were suitable for its decision making.

The company focuses on the population who are unable to take thalidomide

3.4 The company stated that lenalidomide would not be cost effective compared with thalidomide-based therapy, which has a low cost. Therefore, it focused on the comparison of lenalidomide plus dexamethasone with VMP in people unable to tolerate thalidomide or for whom it is contraindicated. The committee was aware that people who cannot take thalidomide have the greatest unmet need among those newly diagnosed with multiple myeloma (see section 3.1). So, it accepted the company's rationale for focusing on this group. However, it recalled that it is unclear how this group is defined in clinical practice (see section 3.2). The committee agreed that, if some people who can take thalidomide have lenalidomide instead (according to the company's argument), this would not be a cost-effective use of NHS resources. Because of this, the committee reiterated that clinicians should evaluate carefully whether people can or cannot take thalidomide.

Clinical evidence

The main source of clinical evidence for lenalidomide plus dexamethasone is the FIRST trial

3.5 The clinical-effectiveness evidence for lenalidomide came from the January 2017 data cut of FIRST. This was an open-label randomised controlled trial comparing lenalidomide plus dexamethasone with MPT. It included:

- 535 people randomised to have lenalidomide plus dexamethasone until progression or unacceptable toxicity and

- 547 people randomised to have MPT.

The trial also included a third arm, lenalidomide plus dexamethasone for a maximum of 18 cycles. However, the company stated that this arm was not relevant to the appraisal because it did not reflect lenalidomide's marketing authorisation. The committee agreed that it did not need to consider this arm of the trial. The ERG considered that FIRST was a large, well-designed and well-conducted trial that included relevant outcome measures and had a long follow up (over 6 years of data). The committee was aware that progression-free survival was the primary end point of the trial and that overall survival was a secondary end point.

The FIRST trial includes only people who can take thalidomide, but the results are generalisable to people who cannot take thalidomide

- 3.6 All patients enrolled in FIRST could, by definition, take thalidomide because the comparator arm of the trial was MPT, which is a thalidomide-based therapy. The committee queried whether the results would be relevant given the company's focus on the population unable to take thalidomide. The clinical experts explained that being unable to take thalidomide would not be expected to change the rates of disease progression or death on lenalidomide seen in the trial. Therefore, they considered the results would be generalisable to the group who cannot have thalidomide. The committee was concerned that the main trial evidence did not reflect the relevant population in this appraisal, but accepted that the results for patients randomised to lenalidomide plus dexamethasone were unlikely to differ markedly in the group who cannot have thalidomide.

The indirect treatment comparison includes people who are able to take thalidomide, but is suitable for decision making

- 3.7 Because there was no trial directly comparing lenalidomide plus dexamethasone with VMP, the company did an indirect treatment comparison to compare them. It included melphalan and prednisone to

complete the network. The ERG considered that the other trials included in the network were methodologically sound, and that the company's statistical approach was appropriate, but there was uncertainty because the network included few trials overall. The committee noted that there was potential for confounding from characteristics that might differ between trials. The clinical experts explained that the main patient characteristics that might affect the clinical outcomes were age, cytogenetics, performance status, chronic kidney disease and frailty. The ERG considered that the trials were similar enough for an indirect treatment comparison. The committee noted that none of the included trials specifically recruited people who were unable to take thalidomide, but concluded that overall the indirect treatment comparison was acceptable for its decision making.

Lenalidomide plus dexamethasone is more clinically effective than VMP

3.8 Based on the results of the indirect comparison, lenalidomide plus dexamethasone improved overall survival compared with VMP (hazard ratio [HR] 0.70, 95% credible interval [CrI] 0.50 to 0.98). For progression-free survival, the hazard ratio for lenalidomide plus dexamethasone compared with VMP was 0.74 (95% CrI 0.52 to 1.05). The committee noted that the wide credible intervals reflected the small number of trials included in the network. It noted that the results for lenalidomide plus dexamethasone taken until progression or unacceptable toxicity compared with lenalidomide plus dexamethasone taken for up to 18 weeks did not differ. Based on the evidence presented, and acknowledging potential confounding, the committee concluded that lenalidomide plus dexamethasone was more clinically effective than VMP, although by how much was uncertain.

Lenalidomide plus dexamethasone is probably well tolerated

3.9 The clinical experts explained that, in their experience of using lenalidomide plus dexamethasone, the treatment is well tolerated and associated with fewer adverse events than VMP or MPT. This is expected

because lenalidomide plus dexamethasone combines 2 drugs, whereas VMP and MPT each combine 3 drugs, 1 of which is cytotoxic. Evidence from FIRST, however, showed that more people who had lenalidomide plus dexamethasone had serious adverse effects than those who had MPT. The company stated that this is because people have lenalidomide plus dexamethasone until disease progression or unacceptable toxicity whereas people have MPT and VMP for a fixed time (72 weeks for MPT and 54 weeks for VMP). Therefore, the committee agreed that lenalidomide plus dexamethasone was likely to be better tolerated in clinical practice than MPT or VMP over the same period of time.

The company's economic model

The company's hybrid model combines Kaplan–Meier data and constant transition probability between states

3.10 The company used a hybrid model structure. This was a partitioned survival model using the Kaplan–Meier data for the first 92 weeks, and thereafter a multi-state Markov model with a constant transition probability between the 3 states: pre-progression, progressed disease and death. The company chose this structure to account for the structural link between disease progression and mortality. The ERG noted that the company's progression-free and overall survival curves generated from the company's model fitted well to the data from FIRST. However, the committee was unclear what advantage the hybrid approach had compared with a partitioned survival model with a parametric curve fitted at week 92. This approach would have allowed different distributions to be tested and the sensitivity of the model to the extrapolation to be better explored. However, the committee acknowledged that there were over 6 years of observed data, which the company's model fitted well.

The company's use of Kaplan–Meier data up to 92 weeks is appropriate

3.11 The committee queried why the company chose 92 weeks as the point at which to apply the Markov model, and asked the ERG if the model's results were sensitive to this cut-off time point. The company stated that it

used the partitioned survival analysis for the first 92 weeks because the log-cumulative hazard plots for progression-free survival from FIRST for each treatment were parallel up to this point then diverged. This was not the case for overall survival because the log-cumulative hazard plots remained parallel, but use of a multi-state Markov model meant that the company had to model progression-free and overall survival in the same way, that is, Kaplan–Meier data up to 92 weeks followed by a constant transition probability matrix. The committee highlighted that a partitioned survival analysis would have allowed more flexible modelling because it would have been possible to model overall and progression-free survival independently. The ERG explained that the model's outputs were not sensitive to the cut-off time point, and that it considered the 92-week cut-off appropriate. The committee concluded that the 92-week cut-off was appropriate. However, it was unclear how sensitive the model was to the structural assumptions that the company chose.

Assumptions used in the economic model

A Weibull curve should be used to extrapolate time on treatment

3.12 To estimate the time on treatment beyond the end of the trial, the ERG noted that the company used different parametric curves to extrapolate the time on treatment of lenalidomide plus dexamethasone and its comparator. The ERG considered that best practice is to use the same parametric curve for both arms, and it preferred the Weibull curve. The committee acknowledged that the model was not sensitive to the change in parametric curve. It considered that using a Weibull curve to extrapolate both arms would be appropriate.

Time on treatment for VMP should be the same as for MPT

3.13 Time on treatment for lenalidomide plus dexamethasone and MPT was collected directly in FIRST. Because there were no data on treatment duration from the clinical trial for VMP, the company assumed that time on treatment in the VMP arm equalled progression-free survival, up to the maximum treatment duration of 54 weeks. The ERG noted that this

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assumption would likely increase the cost of VMP because, in FIRST, progression-free survival was longer than the time on treatment. The ERG noted that the indirect comparison showed that VMP and MPT had the same progression-free survival (HR 1.00, 95% CrI 0.72 to 1.38), and both have a maximum fixed treatment duration. The ERG therefore preferred to assume time on VMP treatment was the same as time on MPT treatment up to the respective maximum treatment durations. The committee considered it plausible that the time on treatment was shorter than progression-free survival because some people would stop treatment because of adverse effects. The committee considered the ERG's change to be appropriate.

The utility estimates should be the same after treatment has stopped

3.14 EQ-5D data were collected directly in FIRST for lenalidomide plus dexamethasone. The company mapped EQ-5D data for VMP from European Organisation for Research and Treatment of Cancer (EORTC) data from the clinical trial. The company assumed that there is a utility decrement during VMP treatment, which would continue even after VMP treatment has finished. The ERG considered there was no good evidence that this difference in utility estimates continued after VMP treatment stopped. The ERG therefore preferred that the utility estimates for lenalidomide plus dexamethasone and VMP to be the same after VMP treatment stops. The committee agreed with the ERG and preferred the utility estimates to be the same for lenalidomide plus dexamethasone and VMP after VMP treatment has stopped.

Treatments taken second line and later in the company's model do not reflect NHS clinical practice, and it is unclear how this would affect the model

3.15 The ERG highlighted that the company modelled the costs and clinical effects of therapies taken second line and later based on data from FIRST. This included thalidomide-based therapies or retreatment with lenalidomide-based therapies in the company's chosen population, that is, those who cannot take thalidomide. This led the committee to conclude

that thalidomide use should not be included in the model. Also, the clinical experts explained that people do not have lenalidomide more than once in clinical practice. The ERG explored removing thalidomide and lenalidomide treatments taken second line and later from the model, but cautioned that it could remove only the costs, but not the effects, of these treatment options. Also, the committee noted that the model did not reflect NHS care because the company did not include the costs and effects of NICE-recommended treatment choices including carfilzomib, panobinostat and pomalidomide-based therapies, which were not available at the time of the clinical trial. The clinical experts were unable to predict what would happen to modelled mortality rates if the model reflected therapies used in the NHS. The committee concluded that the model does not reflect clinical practice, but it was unclear what effect this had on the estimates of cost effectiveness.

Cost-effectiveness estimates

The most plausible ICER is the ERG's preferred ICER

3.16 The company's estimated deterministic incremental cost-effectiveness ratio (ICER) is £11,886 per quality-adjusted life year (QALY) gained for lenalidomide plus dexamethasone compared with VMP, whereas the ERG's preferred estimated deterministic ICER is £19,654 per QALY gained, based on the following changes:

- using a Weibull parametric curve to extrapolate treatment duration (see section 3.12)
- assuming treatment duration was the same for VMP and MPT (see section 3.13)
- assuming utility estimates were the same after VMP treatment had finished (see section 3.14)
- correcting cycle length for VMP utility values and included minor additional administration costs for VMP.

The committee considered the ERG's changes to be reasonable. The Final appraisal determination – Lenalidomide plus dexamethasone for previously untreated multiple myeloma
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committee noted that the cost-effectiveness estimates included inappropriate therapies taken second line and later (see section 3.15). The ERG's exploratory analysis in which the costs of these inappropriate therapies were removed lowered the ERG's ICER. But, because the analysis did not remove their clinical effects, the committee considered this approach to be inappropriate. It concluded that the most plausible ICER was from the ERG's preferred analysis. The committee was aware that both the company's and ERG's ICERs included the new, simple-discount patient access scheme (PAS) in the intervention arm and the existing complex PAS (cost capped after 26 cycles) in the comparator arm to reflect the assumption that the new PAS would take effect only if NICE produces positive guidance. However, the committee was aware that because NHS England had concerns about the operation of the complex PAS, it had renegotiated this scheme with the company. Therefore, the committee considered that there was merit in considering ICERs with the simple-discount PAS applied in both the intervention and comparator arms. The ERG's ICER corresponding with this scenario was £26,713 per QALY gained (the company's ICER was £18,986 per QALY gained).

The ICER is most sensitive to varying the overall survival hazard ratio

3.17 The tornado diagram showed that the ICER was insensitive to varying most parameters, except the hazard ratio for overall survival between lenalidomide plus dexamethasone and VMP. The committee recalled that the credible interval for this parameter in the indirect comparison was wide (see section 3.8). The ERG explored a scenario in which it assumed VMP had a higher overall survival, equal to MPT. The company noted that this scenario was pessimistic because it assumed that the use of therapies second line and later remained unchanged, whereas improving overall survival would increase the use of therapies used second line and later, which would increase costs. The committee was satisfied that the most plausible ICER is reasonably robust to changes in the model parameters.

The cost-effectiveness estimates are only valid if people are unable to take thalidomide

3.18 The company stated that lenalidomide plus dexamethasone was not cost effective compared with the thalidomide-based therapy MPT. The committee recalled that it was unclear how people who cannot take thalidomide are defined in clinical practice (see section 3.2). It reiterated that, if some people have lenalidomide who could take thalidomide, this would not be a cost-effective use of NHS resources. It recalled that people for whom thalidomide is unsuitable can fall into 1 of 2 groups (see section 3.2). The committee concluded it appropriate that these 2 groups be reflected in the recommendation.

Other factors

3.19 The company considered that lenalidomide is innovative because it is taken orally, whereas people have to attend specialist treatment units to have subcutaneous or intravenous bortezomib. The patient experts explained that people would value a new oral treatment because there is a substantial burden of travelling to a specialist treatment unit for injections, particularly for older people or those who travel long distances. The committee considered that the benefit of the oral administration of lenalidomide plus dexamethasone was unlikely to have been fully captured in the QALY, but that it was unlikely to make a substantial difference to its conclusions.

Conclusion

Lenalidomide plus dexamethasone is recommended for routine commissioning for people unable to take thalidomide

3.20 With the committee's preferred assumptions, the ICER was £19,654 (new, simple-discount PAS in the intervention arm and existing complex PAS in the comparator arm) or £26,713 (new, simple-discount PAS in both the intervention and comparator arms) per QALY gained, which is within the range NICE usually considers a cost-effective use of NHS resources. The

committee considered the remaining uncertainties to lie in the model, having included evidence from trials in people who could take thalidomide and treatments in the model taken second line and later not reflecting current clinical practice. The committee recognised that there is an unmet need for new treatment options for this population, and that recommending lenalidomide plus dexamethasone as first line would allow more people to have newer treatments in subsequent lines of therapy. The committee concluded that, despite the uncertainties, lenalidomide plus dexamethasone would be a cost-effective first-line treatment option for people who are not eligible for a stem cell transplant and who cannot take thalidomide. It therefore recommended lenalidomide plus dexamethasone for routine commissioning.

4 Implementation

- 4.1 Section 7(6) of the [National Institute for Health and Care Excellence \(Constitution and Functions\) and the Health and Social Care Information Centre \(Functions\) Regulations 2013](#) requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.
- 4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal determination.
- 4.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has newly diagnosed multiple myeloma, is unable to have a stem cell transplant and the doctor responsible for their care

thinks that lenalidomide is the right treatment, it should be available for use, in line with NICE's recommendations.

5 Review of guidance

- 5.1 The guidance on this technology will be considered for review 3 years after publication. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Amanda Adler

Chair, Appraisal Committee

May 2019

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.

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