

Pomalidomide for multiple myeloma previously treated with lenalidomide and bortezomib

Technology appraisal guidance

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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the [Yellow Card Scheme](#).

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should [assess and reduce the environmental impact of implementing NICE recommendations](#) wherever possible.

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This guidance replaces TA338.

1 Recommendations

- 1.1 Pomalidomide, in combination with low-dose dexamethasone, is recommended as an option for treating multiple myeloma in adults at third or subsequent relapse; that is, after 3 previous treatments including both lenalidomide and bortezomib, only when the company provides pomalidomide with the discount agreed in the patient access scheme.
- 1.2 This guidance is not intended to affect the position of patients whose treatment with pomalidomide 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

- 2.1 Pomalidomide (Imnovid, Celgene) is an immunomodulating agent that has shown an anti-cancer effect in relapsed and refractory multiple myeloma, particularly in patients who have disease that is resistant, or refractory, to previously used anti-myeloma therapies. It is given orally.

Marketing authorisation

- 2.2 Pomalidomide 'in combination with dexamethasone is indicated in the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least 2 prior treatment regimens, including both lenalidomide and bortezomib, and have demonstrated disease progression on the last therapy'.

Adverse reactions

- 2.3 The most common treatment-related adverse events associated with pomalidomide include anaemia, pneumonia, neutropenia, fatigue, pyrexia and thrombocytopenia. For full details of adverse reactions and contraindications, see the summary of product characteristics.

Recommended dose and schedule

- 2.4 The recommended starting dosage of pomalidomide is 4 mg once daily taken orally on days 1 to 21 of repeated 28-day cycles.
- 2.5 The recommended dosage of dexamethasone is 40 mg orally once daily on days 1, 8, 15 and 22 of each 28-day treatment cycle.

Price

- 2.6 £8,884 per 21-tablet pack (excluding VAT; MIMS online and company submission): 1 mg, 2 mg, 3 mg and 4 mg. The average cost of a course of treatment is £44,420.
- 2.7 The company has agreed a patient access scheme with the Department of Health. This scheme provides a simple discount to the list price of pomalidomide, with the discount applied at the point of purchase or invoice. The level of the discount is commercial in confidence. The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS.

3 Evidence

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

4 Committee discussion

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

Nature of the condition

- 4.2 Multiple myeloma is a chronic and ultimately fatal condition that seriously affects quality of life, and treatments that improve both survival and quality of life are important to patients. The clinical experts pointed out that multiple myeloma is a heterogeneous disease; when deciding which treatments to use, response to previous treatments and toxicity are important so having a range of treatment options is valuable. The experts highlighted that there is a clear unmet need in the current treatment pathway, because very few options are available after using existing NICE-recommended treatments (thalidomide, bortezomib and lenalidomide). Moreover, quality of life is an especially important consideration at this stage of the pathway because of the accumulation of toxicities over multiple lines of therapy. The experts highlighted that patients place particular value on therapies that can be taken orally. The committee recognised the need for an effective, well-tolerated treatment option for people with multiple myeloma at third or subsequent relapse who have had at least 3 previous treatments, including both lenalidomide and bortezomib.

Treatment pathway

- 4.3 The committee considered the likely position of pomalidomide with dexamethasone in the treatment pathway for relapsed and refractory multiple myeloma, noting that its marketing authorisation specified that it should only be used after at least 2 previous treatment regimens, including both lenalidomide and bortezomib. The committee was aware that NICE currently recommends

lenalidomide as third-line treatment, and it asked the experts if this reflects clinical practice. The clinical experts confirmed that for most patients, lenalidomide is offered at third line, after thalidomide then bortezomib (they clarified that a small proportion of people had received lenalidomide at second line through the Cancer Drugs Fund). The experts agreed that the evidence for pomalidomide with dexamethasone in this indication was largely for patients whose disease was heavily pre-treated, which was consistent with using it after 3 or more previous therapies. The committee concluded that the appropriate positioning of pomalidomide, in line with clinical practice and the evidence base was after third or subsequent relapse (that is, after 3 previous treatments including both lenalidomide and bortezomib) and that this positioning would be the focus of its considerations.

Comparators

4.4 The committee considered the options available for treating multiple myeloma after third or subsequent relapse. The committee queried whether the comparators included in the scope reflected clinical practice:

- Panobinostat with bortezomib and dexamethasone – The clinical experts stated that panobinostat is used primarily after third relapse and so is an appropriate comparator for pomalidomide. However, they noted that panobinostat is associated with an adverse toxicity profile which is particularly problematic in patients who have already had multiple therapies. The patient expert noted that panobinostat is associated with severe gastrointestinal problems that can severely affect daily activities. The clinical experts also highlighted that for some patients bortezomib may no longer work by this later stage in the pathway. The clinical experts did however acknowledge that if pomalidomide were not available, panobinostat with bortezomib and dexamethasone would likely be the most commonly prescribed treatment regimen.
- Bendamustine with thalidomide and dexamethasone – The clinical experts stated that bendamustine is available on the Cancer Drugs Fund but only when no other treatment alternatives are available.
- Conventional chemotherapy – The experts noted that conventional

chemotherapy would be an option for treating multiple myeloma after third or subsequent relapse, but its use is reliant on the patients' fitness and manageable drug toxicity. Ideally, conventional chemotherapy would be used even later in the treatment pathway after all active agents had been tried.

- 4.5 The experts highlighted that in choosing a treatment, healthcare professionals and patients together consider comorbidities, route of administration, and the response to and toxicity of previous treatments. As such, all of the treatments noted above are used in clinical practice and are appropriate comparators. However, the experts reiterated that none of these treatments is used very often because of the current availability of pomalidomide through the Cancer Drugs Fund. The committee understood the concerns around the comparators and that the clinical experts valued pomalidomide because it was a clinically effective, oral, well-tolerated treatment. The committee concluded that the comparators in the scope were appropriate.

Clinical effectiveness

- 4.6 The committee considered the comparator in MM-003, the main phase III, open-label trial presented by the company. The committee noted that it compared pomalidomide plus low-dose dexamethasone with high-dose dexamethasone alone. It heard from the clinical experts that although high-dose dexamethasone was appropriate when MM-003 was started, it no longer represents an option for active treatment in England. The committee noted that no direct comparative evidence was available for any of the comparators, and recalled its discussions during the previous appraisal about the challenges in obtaining evidence for pomalidomide compared with current therapies. The company presented a case for the clinical effectiveness of high-dose dexamethasone to be used as a proxy for the clinical effectiveness of conventional chemotherapy. The experts noted that despite different toxicity levels, conventional chemotherapy and high-dose dexamethasone have similar delivery mechanisms, and agreed that this was a reasonable assumption. The committee concluded that high-dose dexamethasone was a reasonable proxy for conventional chemotherapy.

- 4.7 The committee discussed the clinical-effectiveness data from MM-003 and its generalisability to clinical practice in England. The committee heard that patients in the trial were younger than typically seen in clinical practice, but the clinical experts' experience in practice suggests that older patients experience similar outcomes with pomalidomide. Moreover, in a subgroup analysis in MM-003, pomalidomide worked as well in older patients as it did in the younger age group. The results, based on the assessment of outcomes by the independent response adjudication committee (median follow-up 10 months), suggested that pomalidomide and low-dose dexamethasone resulted in a statistically significant median progression-free survival gain of 1.8 months compared with high-dose dexamethasone alone (and therefore, by proxy, compared with conventional chemotherapy). The median overall survival gain with pomalidomide and low-dose dexamethasone was between 4.6 months and 7.0 months depending on whether the results were based on the intention-to-treat population or adjusted for crossover (56% of patients crossed over to the pomalidomide arm). The committee concluded that pomalidomide and low-dose dexamethasone is clinically more effective than high-dose dexamethasone alone (and, by proxy, conventional chemotherapy).

Indirect clinical-effectiveness evidence

- 4.8 The committee understood that there was no direct evidence for the comparators other than conventional chemotherapy, and that there was no evidence to support making comparisons using a conventional mixed treatment comparison. The company therefore selected individual treatment arms from available studies and ran separate analyses comparing pomalidomide and low-dose dexamethasone with each of the comparators:
- Bendamustine with thalidomide and dexamethasone – The company included individual patient data from MM-002 for pomalidomide (because it was most comparable to the studies available for bendamustine) and from the MUK-1 trial for bendamustine, supplemented by data on 21 patients from the Gooding and Tarant studies.
 - Panobinostat with bortezomib and dexamethasone – No patient level data were available for panobinostat; so the company conducted a matched adjusted indirect comparison including pooled data from the MM-002,

MM-003 and MM-010 trials for pomalidomide, and data from the PANORAMA-2 trial for panobinostat.

The company also adjusted the comparisons to reflect differences in the characteristics of patients within the datasets available (covariate adjustment).

4.9 The committee discussed the main limitations around these analyses raised by the evidence review group (ERG):

- Only 55 patients had panobinostat so the data are limited.
- Patients in PANORAMA-2 (panobinostat) had on average 1 less line of therapy compared with patients in the MM studies (pomalidomide).
- For the comparison of pomalidomide with bendamustine, the ERG disagreed with the exclusion of the MM-003 and MM-010 trials. The ERG noted that the company had excluded these trials because the assessment of comparability between studies was based mainly on how many people had disease that was refractory to lenalidomide in each study. However, the ERG stated that MM-002 included 3- to 4-times more lenalidomide-refractory patients than the bendamustine studies. Therefore, the ERG was not clear that this justified the exclusion of MM-003 and MM-010, but acknowledged that this did not substantially affect the results.
- The MUK-1 trial included more patients with untreated disease than MM-002 which favoured bendamustine and was not reflective of the population being appraised.

The committee acknowledged that these indirect comparisons were associated with considerable uncertainty but recognised that the company had presented the best evidence available. The committee concluded that the results based on the company's indirect comparisons were acceptable for its decision-making.

4.10 The committee considered the clinical effectiveness of pomalidomide compared with bendamustine.

- Pomalidomide with low-dose dexamethasone resulted in a median of

16.5-month extension of overall survival (95% confidence interval [CI] 12.6 to 19.8) compared with a median of 8.1 months (95% CI 5.3 to 13.5) for bendamustine with thalidomide and dexamethasone, with a statistically significant covariate-adjusted hazard ratio of 0.58.

- Pomalidomide with low-dose dexamethasone was associated with a median progression-free survival benefit of 4.2 months compared with 3.3 months for bendamustine with thalidomide and dexamethasone, with a statistically significant covariate-adjusted hazard ratio of 0.79.

The committee noted that the results were associated with very wide confidence intervals, and also noted the disparity in overall survival results between the pre- and post-progression states. However, on balance, the committee concluded that pomalidomide with low-dose dexamethasone is associated with greater clinical efficacy than bendamustine with thalidomide and dexamethasone.

4.11 The committee considered the clinical effectiveness of pomalidomide compared with panobinostat.

- Pomalidomide with low-dose dexamethasone was associated with a median overall survival benefit of 12.4 months (95% CI 11.1 to 13.4) compared with 17.5 months (95% CI 10.8 to 22.22) for panobinostat with bortezomib and dexamethasone.
- Pomalidomide with low-dose dexamethasone was associated with a smaller median progression-free survival benefit of 4.1 months compared with 5.3 months for panobinostat with bortezomib and dexamethasone.

The committee recalled comments from clinical and patient experts that panobinostat was associated with toxicity, which has a severe effect on quality of life at this stage of the disease. Although panobinostat with bortezomib and dexamethasone appeared to be more effective, the committee recognised that pomalidomide is an oral treatment and concluded that pomalidomide with low-dose dexamethasone is a valuable treatment option at third and subsequent relapse.

Cost effectiveness

- 4.12 The committee considered the cost-effectiveness evidence submitted by the company, noting that the model structure was in line with that used in the previous appraisal. The committee noted that the comments from the ERG around model structure related mainly to identifying and correcting programming errors. The committee agreed that the model structure was appropriate and concluded that it would consider results based on the ERG's correction of errors in the company's base case.
- 4.13 The committee noted that the main change for this review was the inclusion of data from the updated indirect comparisons (see sections 4.7 to 4.10). For the comparison with conventional chemotherapy including data from the MM-030 trial, the company included the data adjusted for crossover using the 2-stage method, and the ERG agreed that this method was most appropriate. The company also included covariate-adjusted comparisons within the model for comparisons with bendamustine and panobinostat, conducted using the corrected group prognosis (CGP) method in the base-case analysis, and the mean of covariates method in a scenario analysis. The ERG included the CGP method in its preferred analysis but did not state that this was a better approach; the committee was aware that it had a small effect on the incremental cost-effectiveness ratios (ICERs). The ERG's main concern with the company's analyses was that because the company used different datasets for pomalidomide in each comparison, a fully incremental analysis was not possible. The ERG preferred to use the pooled dataset for pomalidomide (based on MM-030, MM-002 and MM-010) for all comparisons because it would include a larger dataset and allow for a full incremental analysis. However, the committee noted that this would mean losing the head-to-head trial data compared with conventional chemotherapy, and some of the trial arm comparability for pomalidomide compared with bendamustine. The committee understood the ERG's approach but did not consider that it was more appropriate than the company's approach. The committee concluded that it would base its decisions on the company's base-case ICERs, corrected by the ERG for errors.
- 4.14 Compared with conventional chemotherapy, the company's base-case ICER (corrected by the ERG) for pomalidomide with low-dose dexamethasone was £48,673 per quality-adjusted life year (QALY) gained. The committee was aware

this was based on data directly from the MM-003 trial and was therefore less uncertain than the other comparisons. It concluded that this was the most plausible ICER for pomalidomide with low-dose dexamethasone compared with conventional chemotherapy.

- 4.15 Compared with bendamustine, the company's base-case ICER (corrected by the ERG) for pomalidomide with low-dose dexamethasone was £45,082 per QALY gained. The committee considered that this comparison was likely to be biased in favour of bendamustine, so adjusting for this would lower the ICER. The committee also noted that bendamustine is now available for a lower price (£27 per vial compared with £276 per vial). The ERG stated that accounting for this would increase the ICER. The committee concluded that the ICER for pomalidomide with low-dose dexamethasone compared with bendamustine was associated with uncertainty, but was likely to be less than £50,000 per QALY gained.
- 4.16 The precise ICERs for pomalidomide compared with panobinostat cannot be reported because of a confidential patient access scheme for panobinostat. Based on the company's base case (corrected by the ERG), pomalidomide plus low-dose dexamethasone resulted in cost savings and also a QALY loss, producing ICERs that reflected 'savings per QALY lost'. The committee noted that, in situations in which an ICER is derived from a technology that is less effective and less costly than its comparator, the commonly assumed decision rule of accepting ICERs below a given threshold is reversed. So the higher the ICER, the more cost effective a treatment becomes. The committee recalled the uncertainties underpinning the indirect comparison with panobinostat but was satisfied that the ICER was in the 'southwest' quadrant of the cost-effectiveness plane. Also noting the toxicity associated with panobinostat, the advantages of oral treatment and therefore the improved quality of life associated with pomalidomide, the committee concluded that an additional treatment option would be of value to patients. It further concluded that pomalidomide plus low-dose dexamethasone was recommended as a cost-effective use of NHS resources.

End-of-life considerations

- 4.17 The committee considered the advice about life-extending treatments for people with a short life expectancy in [NICE's final Cancer Drugs Fund technology appraisal process and methods](#).
- 4.18 The company discussed whether life expectancy without pomalidomide would be less than 24 months. The committee noted that median overall survival estimated from the model was 13.10 months for panobinostat, 8.90 months for bendamustine and 6.21 months for conventional chemotherapy. The committee considered that this was also consistent with means below 24 months, and concluded that this criterion was met for all comparisons. It noted, however, that the model was based on trial populations of patients whose disease had been heavily pre-treated. This end-of-life criterion could not, therefore, be assumed to have been met if pomalidomide was positioned any earlier than at third and subsequent relapse in the treatment sequence.
- 4.19 The committee discussed whether a survival benefit of over 3 months can be expected for pomalidomide compared with the comparators. The committee was aware that pomalidomide was less effective than panobinostat (see section 4.10) and therefore did not meet this criterion. The committee noted that pomalidomide was associated with a median overall survival gain of 13.1 months compared with about 6.0 months for conventional chemotherapy and 9.0 months for bendamustine. The committee noted that results were associated with uncertainty, but was satisfied that a survival gain of 3.0 months was plausible. The committee concluded that this end-of-life criterion was met for 2 of the 3 comparisons (that is, compared with bendamustine and conventional chemotherapy).
- 4.20 Having established that pomalidomide meets the end-of-life criteria compared with bendamustine and conventional chemotherapy, the committee recalled that the most plausible ICERs were below £50,000 per QALY gained in both cases. The committee was mindful of the uncertainties underpinning these ICERs, and noted that they were at the upper end of the range normally considered to be cost effective if end-of-life criteria were met. However, the committee acknowledged that the ICERs were based on best available evidence. It recalled testimonies from clinical and patient experts about the significant value of

pomalidomide at this point in the pathway. The committee noted its conclusion in section 4.15 that the savings per QALY lost for pomalidomide compared with panobinostat were high enough for it to be considered a cost-effective use of NHS resources without applying the end-of-life criteria. The committee concluded that it could recommend pomalidomide with low-dose dexamethasone for treating relapsed and refractory multiple myeloma at third or subsequent relapse; that is, after 3 previous treatments including lenalidomide and bortezomib, as a cost-effective use of NHS resources, only when the company provides pomalidomide with the discount agreed in the patient access scheme.

5 Implementation

- 5.1 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.
- 5.2 The Welsh Assembly Minister for Health and Social Services has 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 3 months of the guidance being published.
- 5.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has multiple myeloma and the doctor responsible for their care thinks that pomalidomide is the right treatment, it should be available for use, in line with NICE's recommendations.

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 C](#).

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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