NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

Belantamab mafodotin with bortezomib and dexamethasone for previously treated 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 belantamab mafodotin plus bortezomib and dexamethasone in the NHS in England. The evaluation committee has considered the evidence submitted by the company and the views of non-company stakeholders, clinical experts and patient experts.

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

The evaluation 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 age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Issue date: June 2025

Note that this document is not NICE's final guidance on belantamab mafodotin plus bortezomib and dexamethasone. The recommendations in section 1 may change after consultation.

After consultation:

- The evaluation committee will meet again to consider the evidence, this evaluation consultation document and comments from the stakeholders.
- At that meeting, the committee will also consider comments made by people who are not stakeholders.
- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using belantamab mafodotin plus bortezomib and dexamethasone in the NHS in England.

For further details, see NICE's manual on health technology evaluation.

The key dates for this evaluation are:

- Closing date for comment 3 July 2025
- Second evaluation committee meeting: 3 September 2025
- Details of the evaluation committee are given in section 4

1 Recommendations

1.1 Belantamab mafodotin plus bortezomib and dexamethasone can be used as an option to treat multiple myeloma in adults if they have had 1 previous line of treatment only, which contained lenalidomide, and:

- their condition is refractory to lenalidomide, or
- they cannot tolerate lenalidomide.

Belantamab mafodotin can only be used if the company provides it according to the commercial arrangement (see section 2).

1.2 This recommendation is not intended to affect treatment with belantamab mafodotin plus bortezomib and dexamethasone 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 healthcare professional consider it appropriate to stop.

What this means in practice

Belantamab mafodotin plus bortezomib and dexamethasone must be funded in the NHS in England if it is considered the most suitable treatment option to treat multiple myeloma. It must be funded for adults who have had 1 previous line of treatment only, which contained lenalidomide, and whose condition is refractory to or who cannot tolerate lenalidomide.

Belantamab mafodotin plus bortezomib and dexamethasone must be funded in England within 90 days of final publication of this guidance.

There is enough evidence to show that belantamab mafodotin plus bortezomib and dexamethasone provides benefits and value for money, so it can be used routinely across the NHS in this population.

Why the committee made these recommendations

Belantamab mafodotin plus bortezomib and dexamethasone is licensed for use at second line and beyond. But for this evaluation, the company asked for it to be considered as a treatment at second line.

Usual treatment for multiple myeloma at second line includes:

- daratumumab plus bortezomib and dexamethasone, if lenalidomide is unsuitable or was taken at first line
- selinexor plus bortezomib and dexamethasone, if the multiple myeloma is refractory to daratumumab and lenalidomide
- carfilzomib plus dexamethasone
- carfilzomib plus lenalidomide and dexamethasone.

Evidence from a clinical trial shows that belantamab mafodotin plus bortezomib and dexamethasone increases how long people have before their condition gets worse compared with daratumumab plus bortezomib and dexamethasone. The evidence also suggests that people live longer. But the trial is ongoing, so this is uncertain.

Belantamab mafodotin plus bortezomib and dexamethasone has not been directly compared in a clinical trial with any of the other usual second-line treatments. Indirect comparisons suggest that it is likely to work as well as these, but this is uncertain.

When lenalidomide is not an option at second line, the cost-effectiveness estimates for belantamab mafodotin plus bortezomib and dexamethasone compared with daratumumab plus bortezomib and dexamethasone are within the range that NICE considers an acceptable use of NHS resources.

So, belantamab mafodotin plus bortezomib and dexamethasone can only be used in this population.

2 Information about belantamab mafodotin with bortezomib and dexamethasone

Marketing authorisation indication

2.1 Belantamab mafodotin (Blenrep, GlaxoSmithKline) in combination with bortezomib and dexamethasone is indicated for 'the treatment of adult patients with multiple myeloma who have received at least one prior therapy'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for belantamab mafodotin.

Price

2.3 The list price for belantamab mafodotin is £16,848 per 100-mg vial and £11,784 per 70-mg vial (excluding VAT; company submission).

2.4 The company has a commercial arrangement (simple discount patient access scheme). This makes belantamab mafodotin available to the NHS with a discount. The size of the discount is commercial in confidence.

3 Committee discussion

The evaluation committee considered evidence submitted by GlaxoSmithKline, a review of this submission by the external assessment group (EAG), and responses from stakeholders. See the committee papers for full details of the evidence.

The condition

Multiple myeloma

3.1 Multiple myeloma is a chronic, incurable relapsing and remitting cancer of the plasma cells. Relapsing and remitting means that there can be episodes in which the symptoms worsen, and treatment is needed to bring them back under control. Refractory refers to multiple myeloma that

shows no response to treatment or that has progressed on or within 60 days of the last treatment. Patient experts told the committee that complications from multiple myeloma can be debilitating and have a severe impact on quality of life. The constant possibility of relapse has a huge psychological impact. Patient organisations said that there is a clear need for innovative treatments at second line and beyond that deliver deep, durable responses for people with relapsed and refractory multiple myeloma. The committee recognised the substantial impact multiple myeloma has on survival and quality of life. It acknowledged the unmet need for effective treatments for people with multiple myeloma who have had 1 or more previous treatments.

Treatment pathway

Positioning of belantamab mafodotin plus bortezomib and dexamethasone

3.2 The treatment pathway for multiple myeloma is complex and evolving. Clinical experts said that relapsing–remitting multiple myeloma is challenging to treat because people with the condition are often impacted by side effects from previous treatments and the effects of disease relapse or treatment refractoriness. They said that there is a clear unmet need for treatments that provide longer, more durable remission and manage complications of multiple myeloma.

In its submission, the company proposed belantamab mafodotin plus bortezomib and dexamethasone (Bel-Bor-Dex) as a treatment for adults with multiple myeloma, who have had only 1 previous line of treatment (that is, second line only) and when lenalidomide is unsuitable. This is narrower than the proposed marketing authorisation. The company explained that while there are currently 6 treatment options available at second line, the choice of treatment depends on which treatments people have had at first line. The company said that the number of people having treatment at second line for whom lenalidomide would be suitable would

be small. So, the company suggested that the second-line positioning for people for whom lenalidomide is unsuitable is where Bel-Bor-Dex would address the highest unmet need. Clinical and patient experts suggested that Bel-Bor-Dex would also be beneficial as an option at third line. Clinical advice to the EAG also noted that other treatments may be preferred over Bel-Bor-Dex at second line because of the risk of ocular adverse events with Bel-Bor-Dex.

The committee considered which criteria would apply to lenalidomide being 'unsuitable' and whether the term 'unsuitable' was appropriate and reflected NHS practice. The company said that using 'unsuitable' would support making consistent and equitable recommendations across the multiple myeloma treatment pathways. It noted that previous appraisals had used the term 'unsuitable' to describe lenalidomide (see NICE's technology appraisal guidance on daratumumab with bortezomib and dexamethasone [Dar-Bor-Dex] for previously treated multiple myeloma [TA897]). It said that the main reasons for lenalidomide unsuitability are when the multiple myeloma is refractory to lenalidomide, or when lenalidomide cannot be tolerated because of toxicity. The company also noted that there would be some cases in which healthcare professionals would prefer to offer a non-lenalidomide treatment. Clinical experts agreed that refractoriness and intolerance would be the main reasons for lenalidomide unsuitability. But they said that there would also be cases when lenalidomide was contraindicated, for example in pregnancy. The committee understood that in TA897 lenalidomide was described as unsuitable to mean that people could not tolerate lenalidomide or it was contraindicated or their myeloma was refractory to it. The NHS England Cancer Drugs Fund clinical lead (from here, Cancer Drugs Fund lead) said that the term 'unsuitable' was used differently in practice. They reported that for approximately half of the people who have had Dar-Bor-Dex at second line and not had lenalidomide, the healthcare professional had determined that lenalidomide would be unsuitable. The committee

noted that the recommendations in TA974, a more recently published technology appraisal guidance, includes the term 'refractory to… lenalidomide'. The committee concluded that the terms 'refractory to lenalidomide' and 'cannot tolerate lenalidomide' would provide much clearer guidance to healthcare professionals in the NHS than 'unsuitable'.

The Cancer Drugs Fund lead noted that the situation was likely to change in future. This is because, after publication of NICE's technology appraisal guidance on daratumumab with lenalidomide and dexamethasone (Dar-Len-Dex) for untreated multiple myeloma when a stem cell transplant is unsuitable (TA917), more people would have Dar-Len-Dex at first line. The committee acknowledged that the treatment pathway was rapidly evolving, but that this evaluation should be based on the current treatment pathway. It understood that some people currently having second-line treatment would have started on their treatment pathway before TA917 was published and some would start after.

The committee acknowledged that there is an unmet need for treatment at second line when the person cannot tolerate or their condition is refractory to lenalidomide. But it noted that there was also an unmet need in the wider populations covered by the marketing authorisation. The committee noted it would have expected to see an evidence submission and cost-effectiveness analyses for Bel-Bor-Dex within the full marketing-authorisation population. The committee noted that restricting the population to people whose multiple myeloma is refractory to lenalidomide could potentially exclude people at second line for whom Bel-Bor-Dex would be beneficial but who had not had lenalidomide at first line. It also noted that restricting to lenalidomide being 'unsuitable' would mean that lenalidomide could be a possible treatment option for some people and so should be included as an appropriate comparator (see section 3.3). The committee concluded that the company's proposed initial positioning of second line only and when lenalidomide is unsuitable was not appropriate.

The committee requested the company to provide analyses to evaluate Bel-Bor-Dex within the full marketing authorisation. But if this was not possible, the committee would prefer to evaluate Bel-Bor-Dex in adults with multiple myeloma who have had either:

- only 1 previous treatment (that is, second line only), or
- 1 or 2 previous treatments, with previous exposure to lenalidomide.

In response, the company updated its positioning of Bel-Bor-Dex to be second line only. This includes adults who cannot tolerate or whose condition is refractory to lenalidomide, as per the company's original position. But it also includes people for whom lenalidomide is suitable, as a new subpopulation.

Comparators

3.3 Treatment options for people with newly diagnosed multiple myeloma depend on whether a stem cell transplant is suitable. When the multiple myeloma progresses, treatment options at second line depend on which treatments people have had before and the response to previous treatments (if they were effective or tolerated).

For someone who has had 1 previous line of treatment, currently available options at second line are:

- selinexor plus bortezomib and dexamethasone (see NICE's technology appraisal guidance on selinexor with bortezomib and dexamethasone for previously treated multiple myeloma [TA974])
- Dar-Bor-Dex (see NICE's technology appraisal guidance on daratumumab plus bortezomib and dexamethasone for previously treated multiple myeloma [TA897])
- carfilzomib plus lenalidomide and dexamethasone (see NICE's technology appraisal guidance on carfilzomib with dexamethasone and lenalidomide for previously treated multiple myeloma [TA695])

- carfilzomib plus dexamethasone (see NICE's technology appraisal guidance on carfilzomib for previously treated multiple myeloma [TA657])
- lenalidomide plus dexamethasone (see NICE's technology appraisal guidance on lenalidomide with dexamethasone for multiple myeloma after 1 treatment with bortezomib [TA586])
- bortezomib (see NICE's technology appraisal guidance on bortezomib monotherapy for relapsed multiple myeloma [TA129]).

Because the company proposed Bel-Bor-Dex for second-line use only (see section 3.2), the company provided comparisons with appropriate second-line regimens only:

- Dar-Bor-Dex
- selinexor plus bortezomib and dexamethasone (Sel-Bor-Dex)
- carfilzomib plus dexamethasone (Car-Dex)
- carfilzomib plus lenalidomide and dexamethasone (Car-Len-Dex) incorporating a stopping rule of 18 cycles, in line with TA695.

The company did not explore further populations in line with the marketing authorisation for Bel-Bor-Dex, that is comparators at third line or later. The company did not include bortezomib monotherapy as a comparator because clinical expert advice suggested that this treatment is rarely used in clinical practice. And it did not include lenalidomide plus dexamethasone. The EAG agreed, based on its own clinical advice, that bortezomib monotherapy is not a relevant comparator. It also agreed Car-Len-Dex is likely to supersede lenalidomide plus dexamethasone and so Car-Len-Dex is the most relevant comparator for the lenalidomide suitable population. The committee concluded that the analyses provided by the company for second line only included all relevant comparators.

Clinical effectiveness

Evidence for the proposed population

3.4 Clinical evidence for Bel-Bor-Dex compared with Dar-Bor-Dex came from the DREAMM-7 trial. DREAMM-7 is an ongoing, multicentre, open-label, phase 3 randomised controlled trial. The population includes adults with multiple myeloma who have had at least 1 previous treatment. The company presented data from the intention-to-treat (ITT) population of the trial, which aligns with the proposed population for the marketing authorisation, that is second line onwards. The company used an analysis of the ITT population to inform the clinical and cost effectiveness in its submission. The company originally proposed that for this evaluation, the population should be restricted to people having Bel-Bor-Dex at second line and when lenalidomide is unsuitable(see section 3.2). The company explained that using the ITT data to inform clinical effectiveness for the narrower population was the best approach because the data is more robust than using subgroup data. The company explained that using subgroup data would introduce more uncertainty and would limit the indirect treatment comparisons that can be made with Sel-Bor-Dex and Car-Dex. The EAG acknowledged the company's justification for using the ITT population but noted that the company-proposed restriction is a limitation of the evidence.

The committee noted that the ITT population in DREAMM-7 was younger and fitter than the NHS population. So, the results may not be fully representative of the population eligible for Bel-Bor-Dex in the NHS. The committee also said that using the results from the DREAMM-7 ITT population to inform cost-effectiveness analyses for the company-proposed narrower population may overestimate the benefit of Bel-Bor-Dex in the company-proposed population. The committee concluded it would prefer to see analyses based on evidence from a population that is aligned to the proposed population in this evaluation.

Indirect treatment comparison

3.5 There was no evidence directly comparing Bel-Bor-Dex with Car-Dex, Sel-Bor-Dex or Car-Len-Dex. So, the company presented a Bayesian network meta-analysis (NMA) comparing Bel-Bor-Dex to Car-Dex and Sel-Bor-Dex, as well as to comparators that were not relevant to NHS clinical practice. The networks that included the relevant treatments did not include any loops. This means that the comparisons could not be informed by both direct and indirect evidence, and consistency in the indirect evidence could not be checked. In addition, the committee noted that because the network did not include a single common node, some comparators could only be assessed through intermediary nodes. The EAG reported that the methods used by the company were appropriate but poorly described, and the dataset provided by the company had unexplained differences. It noted that the company's results were not reproducible. Additionally, the EAG identified published evidence describing a later data cut-off for one of the trials than was used in the company submission (LEPUS, which compared Dar-Bor-Dex with Bor-Dex). The EAG updated the analyses, and noted that this did not dramatically change the results. The company agreed with using the EAG-updated analyses. For the comparison with Car-Len-Dex, the company presented an unanchored matching-adjusted indirect comparison (MAIC) using data from DREAMM-7 for Bel-Bor-Dex and ASPIRE for Car-Len-Dex. The EAG highlighted the considerable uncertainty with the unanchored MAIC but said that the limitations were adequately described and explored by the company. The committee concluded that the company's NMAs and unanchored MAIC were uncertain but were suitable for decision making but that the NMA should include the most recent data cut-off from LEPUS

Clinical-effectiveness results

3.6 From DREAMM-7 (see section 3.4), Bel-Bor-Dex showed for the full ITT population, (that is one or more prior lines of treatment, including

lenalidomide-exposed, not exposed, and lenalidomide-refractory), a statistically significant improvement in overall survival (HR 0.57; 95% CI 0.40 to 0.80) and progression-free survival (HR 0.41; 95% CI 0.31 to 0.53) compared with Dar-Bor-Dex.

From the indirect treatment comparisons (see section 3.5), Bel-Bor-Dex showed:

- a statistically significant improvement in progression-free survival compared with Dar-Bor-Dex, Car-Dex, Sel-Bor-Dex and Car-Len-Dex (the company considers the exact data to be confidential and so it cannot be reported here)
- a statistically significant improvement in overall survival compared with Dar-Bor-Dex, Car-Dex, Sel-Bor-Dex and Car-Len-Dex (the company considers the exact data to be confidential and so it cannot be reported here).

Exposure to belantamab mafodotin

3.7 The summary of product characteristics (SmPC) for belantamab mafodotin (see section 2) lists the starting dose as 2.5 mg/kg once every 3 weeks. In cases of moderate or severe ocular side effects, the SmPC states that belantamab mafodotin should be withheld until there is observed improvement in both corneal examination findings and best corrected visual acuity to 'mild severity or better'. Belantamab mafodotin can then be resumed at a reduced dose of 1.9 mg/kg once every 3 weeks. In the DREAMM-7 safety population, the mean dose was lower than the SmPC-recommended reduced dose (the company considers the actual dose to be confidential, so it cannot be reported here). The company analyses included dose reductions and delays based on DREAMM-7 individual patient data to inform costs of belantamab mafodotin in the model. The EAG said that while this approach was reasonable, EAG clinical experts noted that healthcare professionals are likely to be cautious with dosing because of potential side effects and would consider

starting treatment on a lower dose. The clinical experts at the committee explained that they would start most people on the 2.5 mg/kg dose. Company clinical advice at clarification also suggested that healthcare professionals may choose to start with a dosing window of every 4 weeks, extending to every 8 weeks and then every 12 weeks. So, exposure to belantamab mafodotin may be lower in NHS clinical practice, which is not accounted for in the company submission. The EAG noted that costs for belantamab mafodotin were sensitive to whether delays were captured or not. But it also noted that the impact on effectiveness was unknown and so could not be explored in the model. The clinical experts gave their experience of using belantamab mafodotin in practice, in which some people had delays to dosing of up to 6 months with no loss of response. The committee noted that subgroup data for people who had belantamab mafodotin at 8 to 12-week intervals was not included in the company submission. In response the company explained that based on data from 15 months after the first dose in DREAMM-7, people in the trial had a median of 9 to 12 weeks between doses. It also explained that modified progression-free survival in the ITT population of DREAMM-7 was similar to people with a dosing schedule extended to 12 weeks or more. The EAG noted that the assumption of no change in efficacy with longer dosing interval is likely to be reasonable but the evidence was limited. The committee recalled that the company used individual patient data to inform belantamab mafodotin costs, but did not use individual patient data for the comparators and instead used relative dose intensity (RDI). The company explained that RDI for comparators remained high and individual patient data was not available for some comparators. So, it did not think that using RDI for comparators instead of individual patient data would make a difference to the results. The EAG agreed that daratumumab dosing is likely to be constant and less variable than belantamab mafodotin. The EAG noted it is likely that RDI is appropriate to model dosing of daratumumab and individual patient data would have a small impact on the cost-effectiveness result. The committee agreed that using

individual patient data from DREAMM-7 to inform dosing of belantamab mafodotin and RDI to inform dosing for other comparators may be appropriate. But it noted the uncertainty of using different metrics to inform dosing for belantamab mafodotin and its comparators.

Cost effectiveness

Company's modelling approach

3.8 The company provided a cohort-based partitioned survival model to estimate the cost effectiveness of Bel-Bor-Dex compared with Dar-Bor-Dex, Car-Dex, Sel-Bor-Dex and Car-Len-Dex. The model included 4 health states: progression free on treatment, progression free off treatment, progressed disease, and death. Progression free was split into the on-treatment and off-treatment health states because some people in DREAMM-7 withdrew from active treatment before disease progression, which resulted in different costs and consequences. The probability of being in each health state was calculated using extrapolated progression-free survival, overall survival and time to treatment discontinuation. The model used a cycle length of 1 week over a lifetime horizon of 36 years (the starting age in the model was 64 years). The committee concluded that overall, the company's model structure was acceptable for decision making. But it noted that the starting age used in the model, based on the age in DREAMM-7, was younger than would be expected in clinical practice. The company updated its model to include a starting age that reflects the NHS population based on Dar-Len-Dex data from the Systemic Anti-Cancer Therapy (SACT) dataset.

Overall survival predictions

3.9 Because DREAMM-7 is still ongoing, clinical data on long-term outcomes is unknown. So, the company extrapolated overall-survival data by fitting independent parametric models to the observed data. For Dar-Bor-Dex, a Weibull parametric fit was applied, informed by the more mature data available from the Dar-Bor-Dex arm of the CASTOR trial. To justify fitting

independent models to the overall-survival data, the company said that there was inconclusive evidence about the appropriateness of assuming proportional hazards in the DREAMM-7 data. There appeared to be time points where the cumulative hazards for the 2 treatments cross, which would usually be a reason to reject proportional hazards assumptions. But a formal test for nonproportionality was not significant and the Schoenfeld residuals did not deviate from an expected pattern, which is when proportional hazards would apply. The committee noted that the timepoints where the cumulative hazards cross were in the first few months of follow up, when few events had occurred. The committee said that this should not rule out the use of an approach that assumes proportional hazards. Overall-survival curves for comparators were calculated by applying hazard ratios from the NMA to the extrapolated Dar-Bor-Dex curve. The EAG considered this approach to be appropriate. The committee recalled that data from DREAMM-7 was based on the ITT population, which may not be reflective of the subgroup proposed by the company (see section 3.4). So, it concluded that the overall-survival extrapolations may not be representative of overall survival in the population proposed by the company. The committee suggested that it would be possible to use alternative models. These could provide more accurate overall-survival estimates in the relevant population and reduce the uncertainty between the immature survival data and long-term predictions. The committee noted it would prefer to see updated analyses applying the relative effects of DREAMM-7 to SACT data for Dar-Bor-Dex to generate overall survival for Bel-Bor-Dex and its comparators in the most relevant population. It noted that such data had been collected and reported recently in a conference abstract (Lawton et al. 2024). The company updated its analyses to include SACT data as a reference for the Dar-Bor-Dex arm (baseline curve) with relative treatment effects being informed by DREAMM-7 and applied to the SACT baseline curve. The committee concluded the company updated approach using SACT data was appropriate.

Utility values

3.10 In the company submission, progression-free utilities were informed by DREAMM-7 EQ-5D-3L data. The company used a higher utility value for Bel-Bor-Dex than the comparators for the progression-free health states. The EAG noted that the approach to apply treatment-dependent utility values, rather than based on the line of treatment, was appropriate and an approach taken by previous NICE evaluations. But it said that the company had not provided empirical evidence to support the assumption that Bel-Bor-Dex would have a higher utility than its comparators. It considered an alternative assumption that the same progression-free health-state utility as the comparators would be just as plausible. The EAG explored this in a scenario analysis and reported that it did not have a material impact on the cost-effectiveness results. The committee acknowledged this but highlighted that there is no interaction term between Bel-Bor-Dex and the progression-free health state. It explained that the interaction term is an important factor in assessing improved health-related quality of life. It said that this is because a higher quality-adjusted life year (QALY) is expected the longer time is spent in the progression-free health state. It noted that a simpler model that does not assume a difference by treatment may be a better fit.

For the comparator treatments, the company modelled a higher utility value for the progressed-disease than progression-free health state. (The company considers the exact values to be confidential, so they cannot be reported here). This meant that people with progressed disease had a better quality of life. The EAG highlighted that the higher utility value for progressed disease was not clinically plausible. It also said that the utilities provided by the company did not take into account line of treatment. It proposed applying a utility decrement to the progressed-disease health state for the comparators, calculated from Hatswell (2019). At the committee meeting, the company agreed that the utilities in the company submission lacked validity and there was no difference in EQ-5D

between the comparators. The committee noted that the utility values were generally higher than expected. It suggested that this may have been caused by the DREAMM-7 population being younger and fitter than the NHS population (see section 3.4). The committee agreed that higher utility values for the progressed-disease than progression-free health state was implausible. The committee recalled that the company had not provided sufficient evidence to suggest a treatment-specific utility benefit for Bel-Bor-Dex. The committee concluded that it preferred to apply utility values independent of treatment arm based on the health state only (progressed disease and progression free). The company updated its base case to apply treatment-independent utility values that were informed directly by DREAMM-7 for the progression-free health state. It then applied a utility decrement upon progression, based on Hatswell (2019) to the progression-free health state to derive the progressed-disease health-state utility value. The committee concluded that the company's updated approach was appropriate.

Ocular adverse events and health-related quality of life

3.11 In DREAMM-7, EQ-5D-3L scores at last follow up were the same across the Bel-Bor-Dex and Dar-Bor-Dex groups, and there was no significant difference between baseline and final follow up. The EAG's clinical adviser noted that quality of life is likely to be negatively affected for some people in the Bel-Bor-Dex arm who experience adverse events. Corneal adverse events relating to study treatment were more common with Bel-Bor-Dex than Dar-Bor-Dex (the data was considered confidential by the company so cannot be reported here). The model included treatment-specific ocular adverse events of grade 3 and above, including keratopathy, blurred vision and dry eyes. These adverse events were only applied to the Bel-Bor-Dex arm. The EAG noted that the incidence of keratopathy applied in the model was much lower than the incidence in DREAMM-7. In addition, the adverse events were applied as a one-off quality-of-life decrement to the first cycle in the model, using disutilities sourced from NICE's technology appraisal guidance on ciclosporin for

treating dry eye disease that has not improved despite treatment with artificial tears. The EAG said that applying the adverse events as a one-off may not be appropriate to capture adverse events that occur later or are experienced for a longer length of time. It also noted that time to onset and duration of events of grade 3 and above were not reported.

The committee discussed whether EQ-5D-3L was sensitive enough to capture the impact on quality of life of ocular side effects and visual impairment with Bel-Bor-Dex. The clinical experts, along with the patient and expert submissions, advised that belantamab mafodotin is well tolerated, and that people are prepared to tolerate the ocular side effects. The clinical experts at committee thought that EQ-5D-3L is a reasonable tool to capture the impact of ocular side effects on quality of life. In addition, the committee noted that patient experts said that the EQ-5D-3L in the trial would have likely captured the impact of ocular adverse events on health-related quality of life, given the frequency of assessments.

The committee noted that although EQ-5D-3L is not disease-specific, it allows for consistent evaluations across disease areas and the concern about sensitivity could apply to many conditions. But it acknowledged that the extent to which EQ-5D-3L captures the impact of vision loss on quality of life is uncertain. So, the committee concluded that a disutility for ocular adverse events should be included in the base case with scenarios exploring the impact of excluding a disutility for ocular adverse events.

Cost of subsequent treatments

3.12 The company applied different costs for the subsequent treatments in the model, as a one-off cost to each cycle, which was proportional to the number of people entering the progressed-disease health state. Subsequent costs were the same for Bel-Bor-Dex, Car-Dex and Sel-Bor-Dex, but differed for Dar-Bor-Dex. The company considered 3 distributions, which were aligned to the:

- NICE treatment pathway
- current treatment pathway in NHS practice, or
- likely future treatment pathway.

It said that the most appropriate distribution to use was to align treatments with the current pathway in NHS practice. The EAG said that the key driver affecting costs of subsequent treatments was the delay to disease progression rather than the actual distribution of treatments. So, the EAG preferred to apply the same distribution of treatments after disease progression, across all comparators. The committee said that applying different subsequent treatment distributions and costs to each treatment arm based on the current treatment pathway was appropriate. But it noted that the subsequent treatment teclistamab was not included in the company submission. The company said that this was because teclistamab was still under NICE evaluation at the time of submission. (See NICE's technology appraisal guidance on teclistamab for treating relapsed and refractory multiple myeloma after 3 or more treatments). The committee acknowledged that the multiple myeloma pathway is rapidly evolving (see section 3.2) but agreed that because teclistamab has had a positive recommendation from NICE it was now part of standard practice. The company updated its base case to include teclistamab as a subsequent treatment. The committee noted the inclusion of teclistamab in the model only impacts subsequent treatment costs. It was concerned there may be a loss of benefit with teclistamab at fourth line because it works in a similar way to belantamab. It noted there was a lack of evidence on the impact of belantamab treatment at second line on effectiveness of teclistamab fourth line. It concluded that the analyses should be updated to include teclistamab as a subsequent treatment. It also requested a scenario analysis in which all subsequent treatment costs are applied in the same way for each intervention.

Monitoring costs

3.13 In its base case, the company assumed that people having Bel-Bor-Dex would be seen by an ophthalmologist for only the first 4 treatment cycles as per the draft SmPC, at a resource use per model cycle of 0.33. The company considered that this was likely to be an overestimate given that dose delays are common and so people would likely see an ophthalmologist fewer than 4 times over the first 4 treatment cycles. The EAG noted that the SmPC also states further visits can occur if clinically indicated. But it said this could potentially be captured by the adverse-events costs. The company suggested that including additional ophthalmologist visits in addition to adverse-events costs could result in double counting. On this basis, the EAG suggested the company's assumptions for resource use and costs were reasonable.

The Cancer Drugs Fund lead explained that the ophthalmic monitoring needed for belantamab mafodotin would likely be burdensome for ophthalmology departments in the NHS, which has long waiting lists. They explained that delays in implementation would be likely. They highlighted that everyone must have an ophthalmic eye exam before each of the first 4 doses of belantamab mafodotin, and subsequent monitoring in the event of ocular adverse events. They explained that the mechanism of delivery of this monitoring service and the method of communication between ophthalmology departments or community services and oncologists was unclear. The clinical experts highlighted that about 30 to 40 hospitals took part in the compassionate-use scheme for belantamab mafodotin, and so hospitals have a pathway in place for eye examinations. The company explained that between 2018 and 2024, over 100 NHS sites administered belantamab mafodotin in different settings. It explained that the company is exploring the option of supporting people through access to community-based ophthalmology at the point of recommendation. The committee recalled that the incidence and costs of ocular adverse events were applied as a one-off in the model, and the incidence of keratopathy applied in the model was lower than observed in DREAMM-7 (see

section 3.11). It also recalled that time to onset and duration of adverse events of grade 3 and above was not reported. The committee said that there was uncertainty as to whether the cost of ocular adverse events had been adequately accounted for in the model. It said that this was because the model had not included continued monitoring until resolution of ocular adverse events. So, the cost of monitoring with belantamab mafodotin was likely to have been underestimated. It concluded that the base case should include the cost of monitoring ocular adverse events using hospital-based ophthalmology services, with a scenario analysis provided using the community-based ophthalmology services proposed by the company.

Severity

3.14 NICE's methods about conditions with a high degree of severity did not apply.

Cost-effectiveness estimates

The committee's preferred assumptions

3.15 The company accepted the committee's preferred assumptions which include:

- evaluating Bel-Bor-Dex within its full marketing authorisation, or if not possible, at second-line only without a lenalidomide precondition (see section 3.2)
- using a later data cut from the LEPUS study (see section 3.5)
- using individual patient data for Bel-Bor-Dex and RDI for other comparators (see section 3.7)
- using a baseline age that is reflective of the NHS population, from the SACT dataset (see section 3.8)
- using Dar-Bor-Dex SACT data to inform the baseline overall-survival curve with relative effects applied for Bel-Bor-Dex and other comparators (see section 3.9)
- using treatment-independent utility values (see section 3.10)

- including disutilities from ocular adverse events for Bel-Bor-Dex (see section 3.11)
- including teclistamab as fourth-line treatment (see section 3.12)

Acceptable ICER

3.16 NICE's manual on health technology evaluations notes that, above a most plausible incremental cost-effectiveness ratio (ICER) of £20,000 per QALY gained, judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. But it will also take into account other aspects including uncaptured health benefits. The committee noted the high level of uncertainty, specifically that:

- the indirect treatment comparisons were based on an unanchored MAIC (see section 3.5)
- exposure to belantamab mafodotin may be lower in clinical practice (see section 3.7)
- the long-term predictions of overall survival for belantamab mafodotin are uncertain (see section 3.8).

Because of these uncertainties and accounting for the unmet need, the committee concluded that an acceptable ICER would be around the middle of the range NICE considers a cost-effective use of NHS resources (£20,000 to £30,000 per QALY gained; see section 3.17).

Cost-effectiveness results

3.17 The committee considered the cost effectiveness of Bel-Bor-Dex compared with Dar-Bor-Dex, Sel-Bor-Dex and Car-Len-Dex in the relevant populations at second line only, incorporating all of its preferred assumptions (see section 3.15). The exact ICERs cannot be reported here because some prices are confidential. For the comparison with Dar-

Bor-Dex when lenalidomide is not an option at second line, the deterministic and probabilistic ICERs for Bel-Bor-Dex were within the range considered to be a cost-effective use of NHS resources. For the comparison with Sel-Bor-Dex, when daratumumab and lenalidomide are not an option at second line, the deterministic and probabilistic ICERs for Bel-Bor-Dex were above the range considered to be a cost-effective use of NHS resources. For the comparison with Car-Len-Dex, when lenalidomide is an option at second line, the deterministic and probabilistic ICERs for Bel-Bor-Dex were above the range considered to be a cost-effective use of NHS resources.

Other factors

Equality

3.18 The committee considered that the company's proposed restrictions may create inequalities in treatment access. The committee reiterated its preference to evaluate Bel-Bor-Dex within its full marketing authorisation, that is second line onwards. It thought that restricting a recommendation to second line only may disadvantage people with multiple myeloma at third line and later. It also considered that restricting the recommendation to people who had not had lenalidomide would disadvantage people who had not been offered this treatment at first line. The committee noted the company had updated its proposed population to be second line only and provided comparisons against all relevant comparators at second line. Because the cost-effectiveness estimates compared with some comparators were higher than the range considered to be a cost-effective use of NHS resources, Bel-Bor-Dex could not be recommended for the full second line only population. While the committee believes that Bel-Bor-Dex not being cost-effective against all comparators at second line will have the effect of disadvantaging some patients with multiple myeloma, the committee did not consider this to be a formal equality issue because it does not relate to any of the protected characteristics under the Equality Act 2010.

The committee also considered that the prevalence of multiple myeloma is higher in people from Black ethnic backgrounds. But the Cancer Drugs Fund clinical lead confirmed that 4.5% of people diagnosed with multiple myeloma in England are Black which is the proportion in the general UK population. So, the committee did not think that an optimised recommendation would increase or reduce any health inequalities.

Uncaptured benefits

3.19 The committee considered whether there were any uncaptured benefits of Bel-Bor-Dex. It did not identify additional benefits of Bel-Bor-Dex not captured in the economic modelling. So, the committee concluded that all additional benefits of Bel-Bor-Dex had already been taken into account.

Conclusion

Recommendation

3.20 The committee noted that the ICERs for Bel-Bor-Dex compared with Dar-Bor-Dex were within the range considered to be a cost-effective use of NHS resources. It also noted that the ICERs for Bel-Bor-Dex compared with Sel-Bor-Dex and Car-Len-Dex were above the range considered to be a cost-effective use of NHS resources. So, Bel-Bor-Dex can be used for routine commissioning in the NHS for adults with multiple myeloma if they have had 1 previous line of treatment only and they cannot tolerate, or their condition is refractory to lenalidomide.

4 Evaluation committee members and NICE project team

Evaluation 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 technologies being evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The minutes of each evaluation committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Chair

Charles Crawley
Chair, technology appraisal committee B

NICE project team

Each evaluation is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the evaluation), a technical adviser, a project manager and an associate director.

Lauren Elston
Technical lead

Nigel Gumbleton
Technical adviser

Vonda Murray
Project manager

Richard Diaz
Associate director

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