NICE National Institute for Health and Care Excellence

NICE guidance

Isatuximab with pomalidomide and dexamethasone for treating relapsed and refractory multiple myeloma

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.

Contents

1 Recommendations

1.1 Isatuximab, plus pomalidomide and dexamethasone, is recommended for use within the Cancer Drugs Fund as an option for treating relapsed and refractory multiple myeloma in adults who have had lenalidomide and a proteasome inhibitor, and whose disease has progressed on their last treatment, only if:

- they have had 3 previous lines of treatment
- the conditions in the managed access agreement for isatuximab plus pomalidomide and dexamethasone are followed.

1.2 This recommendation is not intended to affect treatment with isatuximab plus pomalidomide 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 clinician consider it appropriate to stop.

Why the committee made these recommendations

The company proposes that isatuximab plus pomalidomide and dexamethasone is used only for people who have already had 3 lines of treatment. Although effective options after 2 lines of treatment are also needed, the clinical- and cost-effectiveness data for isatuximab plus pomalidomide and dexamethasone at this point in the treatment pathway are not suitable for decision making.

After 3 lines of treatment, people usually have pomalidomide plus dexamethasone, or daratumumab alone (in the Cancer Drugs Fund). Clinical trial evidence suggests that isatuximab plus pomalidomide and dexamethasone delays the disease progressing and increases how long people live compared with pomalidomide plus dexamethasone. But, the trial is not finished so the benefit in the longer term is uncertain.

The cost-effectiveness estimates for isatuximab plus pomalidomide and dexamethasone after 3 previous lines of treatment are uncertain because of limitations in the clinical data. The estimates are higher than what NICE normally considers an acceptable use of NHS resources. So isatuximab plus pomalidomide and dexamethasone cannot be

recommended for routine use in the NHS.

Collecting more data from the ongoing trial and from NHS practice would help to address some of the uncertainties. Isatuximab plus pomalidomide and dexamethasone could be cost effective after 3 previous lines of treatment when the company's commercial offer as part of a managed access agreement is used. Therefore, isatuximab plus pomalidomide and dexamethasone is recommended for use in the Cancer Drugs Fund.

2 Information about isatuximab

Marketing authorisation indication

2.1 Isatuximab (Sarclisa, Sanofi) in combination with pomalidomide and dexamethasone has a marketing authorisation 'for the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least 2 prior therapies including lenalidomide and a proteasome inhibitor and have demonstrated disease progression on the last therapy'.

Dosage in the marketing authorisation

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

Price

2.3 The proposed list price for isatuximab in the company submission is £506.94 for a 100-mg vial or £2,534.70 for a 500-mg vial. The company has a commercial arrangement. This makes isatuximab 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.

3 Committee discussion

The appraisal committee considered evidence submitted by Sanofi, a review of this submission by the evidence review group (ERG), the technical report, and responses from stakeholders. See the committee papers for full details of the evidence.

The appraisal committee was aware that several issues were resolved during the technical engagement stage, and agreed that:

- The model time horizon should be 20 years to capture all benefits and costs of the intervention and the comparators.
- The company's amendment to the probabilistic sampling of health utility data, which ensures that the utility value for the progressed disease health state does not exceed the utility value for the progression-free disease health state, is appropriate.
- The company's amendment to its model, which applies drug costs at the start of each cycle, is appropriate.

The committee recognised that there were remaining areas of uncertainty associated with the analyses presented (see technical report, table 4, page 40), and took these into account in its decision making. It discussed the issues that were outstanding after the technical engagement stage.

The condition

People with relapsed and refractory multiple myeloma would welcome a new effective treatment option

3.1 Multiple myeloma is an incurable and progressive condition that affects survival and quality of life. The patient experts explained that it causes severe symptoms, which have a significant impact on patients' quality of life and are also challenging for carers. They highlighted the psychological impact for patients approaching the end of the treatment pathway, where further treatment options are limited. The committee was aware that clinicians value having a range of different

treatment options for patients. One patient expert noted that although some treatments are oral and people can take them at home, some people prefer to have their treatment in hospital. He also highlighted that patients value treatments that delay the disease progressing, which outweighs the negative impact of their side effects. The committee recognised the need for effective treatment options for previously treated multiple myeloma, and concluded that people would welcome a new treatment option.

Treatment pathway

The treatment pathway for multiple myeloma is rapidly evolving

3.2 Treatment options for multiple myeloma depend on how many previous lines of treatment a person has had, the specific treatments, their response to these treatments, and their preferences. If a stem cell transplant is suitable:

- Induction treatment is bortezomib, given before the transplant.
- After 1 previous line of treatment, people may have bortezomib again, along with a second stem cell transplant.

If a stem cell transplant is not suitable:

- For untreated disease, treatments include thalidomide or bortezomib plus an alkylating agent, for example, melphalan or cyclophosphamide, and a corticosteroid, for example, dexamethasone. Lenalidomide plus dexamethasone is also an option when thalidomide is not appropriate.
- After 1 previous line of treatment, options include lenalidomide plus dexamethasone if the person has had bortezomib before, or carfilzomib plus dexamethasone if they have not had bortezomib before. Also, daratumumab plus bortezomib and dexamethasone is available in the Cancer Drugs Fund.

After this, the options do not depend on whether a stem cell transplant is suitable:

- After 2 previous lines of treatment, options include lenalidomide plus

dexamethasone or panobinostat plus bortezomib and dexamethasone. Also, ixazomib plus lenalidomide and dexamethasone is available in the Cancer Drugs Fund.

- After 3 previous lines of treatment, options include pomalidomide plus dexamethasone or panobinostat plus bortezomib and dexamethasone. Daratumumab alone or ixazomib plus lenalidomide and dexamethasone are available in the Cancer Drugs Fund.

  Isatuximab plus pomalidomide and dexamethasone can be used whether or not people have had a stem cell transplant. The clinical experts explained that, following recent NICE guidance, the use of lenalidomide plus dexamethasone for untreated disease and the use of daratumumab plus bortezomib and dexamethasone after 1 previous line of treatment is increasing. The committee understood that the multiple myeloma pathway is rapidly evolving.

The company positions isatuximab plus pomalidomide and dexamethasone after 3 previous lines of treatment

3.3 The marketing authorisation for isatuximab plus pomalidomide and dexamethasone states that it must be used after lenalidomide and a proteasome inhibitor, which means after 2 previous lines of treatment or later. Proteasome inhibitors include bortezomib, carfilzomib and ixazomib. But the marketing authorisation does not specify the position in the treatment pathway. The company chose to position isatuximab plus pomalidomide and dexamethasone after 3 previous lines of treatment. It did this based on unmet clinical need and advice from clinical experts. The committee noted that the company's positioning meant that the population was narrower than defined by both the marketing authorisation and NICE's final scope. The clinical expert explained that to have isatuximab plus pomalidomide and dexamethasone, a person must have had lenalidomide. But currently many clinicians use lenalidomide after 2 previous lines of treatment, with ixazomib and dexamethasone in the Cancer Drugs Fund, or with dexamethasone. Therefore, the clinical experts agreed that the company's positioning was appropriate. The committee concluded at its first meeting that it would focus its discussion on people who have had 3 previous lines of treatment.

There is unmet need for new effective options after 2 previous lines of treatment

3.4 The committee recalled that for isatuximab plus pomalidomide and dexamethasone both the marketing authorisation and NICE's final scope included people who have had at least 2 previous lines of treatment, to include lenalidomide and a proteasome inhibitor. It also recalled that lenalidomide and bortezomib are now options for untreated multiple myeloma and after 1 previous line of treatment (see section 3.2). The patient expert explained that patients would prefer any NICE recommendation to include the population covered by the marketing authorisation rather than restrict it to those who have had 3 previous lines of treatment. The Cancer Drugs Fund clinical lead explained at the first meeting that lenalidomide and a proteasome inhibitor is now being used more often at earlier points in the treatment pathway. This has meant that there is an increasing need for new and effective options after 2 previous lines of treatment. In response to the committee's request at the first meeting, the company did a cost-effectiveness analysis for isatuximab plus pomalidomide and dexamethasone after 2 previous lines of treatment compared with the comparator in NICE's final scope (see section 3.24). The committee concluded that there is unmet need for new effective treatment options for people who have had 2 previous lines of treatment.

Comparators

After 3 previous lines of treatment, pomalidomide plus dexamethasone is the only relevant comparator

3.5 NICE guidance recommends both pomalidomide plus dexamethasone and panobinostat plus bortezomib and dexamethasone after 3 previous lines of treatment for multiple myeloma. NICE's final scope for this appraisal lists these as the comparators. The committee recalled that treatments recommended in the Cancer Drugs Fund are not considered to be comparators. The company did not consider panobinostat plus bortezomib and dexamethasone to be a relevant comparator to isatuximab plus pomalidomide and dexamethasone after 3 previous lines of treatment. It explained that this was because of toxic adverse

effects and the lack of perceived efficacy noted by clinicians it consulted, which means it is usually used after 4 previous lines of treatment. To comply with NICE's final scope, the company compared the clinical and cost effectiveness of isatuximab plus pomalidomide and dexamethasone with panobinostat plus bortezomib and dexamethasone and pomalidomide plus dexamethasone. The comparison with panobinostat plus bortezomib and dexamethasone included an indirect treatment comparison for clinical effectiveness because there was no trial directly comparing the 2 treatments. The ERG noted that 1 of its clinical advisers agreed with the company's position, but 2 other advisers stated that panobinostat plus bortezomib and dexamethasone is used after 3 previous lines of treatment and toxicity is managed by adjusting the dose. The clinical experts at the meeting explained that daratumumab, available in the Cancer Drugs Fund, or pomalidomide plus dexamethasone are the most commonly used options after 3 previous lines of treatment. They stated that panobinostat plus bortezomib and dexamethasone is very rarely used after 3 previous lines of treatment because of toxicity and perceived poor clinical efficacy. The Cancer Drugs Fund clinical lead explained that clinicians can now offer bortezomib again without having to use it with panobinostat and that few clinicians offer panobinostat plus bortezomib and dexamethasone after 3 previous lines of treatment. The committee concluded that after 3 previous lines of treatment, pomalidomide plus dexamethasone is the only relevant comparator.

Clinical evidence

The evidence for people who have had 3 previous lines of treatment is acceptable for decision making

3.6 ICARIA-MM is an open-label randomised trial, comparing isatuximab plus pomalidomide and dexamethasone with pomalidomide plus dexamethasone. It included people with relapsed and refractory multiple myeloma who have had at least 2 previous lines of treatment, including lenalidomide and a proteasome inhibitor. The primary outcome was progression-free survival. Because the company positioned isatuximab plus pomalidomide and dexamethasone as a treatment option after 3 previous lines of treatment, it provided clinical-effectiveness data from a post hoc subgroup of people from ICARIA-MM who had

3 previous lines of treatment. The committee was aware that this subgroup was not stratified and therefore not a randomised group. The ERG noted that there was more uncertainty associated with the subgroup results than with the randomised population results, indicated by wider confidence intervals. The committee understood the limitations of the subgroup analysis for people who have had 3 previous lines of treatment, but agreed to accept it for decision making.

Isatuximab plus pomalidomide and dexamethasone likely extends both progression-free and overall survival, but the data are immature

3.7 ICARIA-MM is ongoing. At the interim data cut (October 2018), median follow up was 11.6 months in the trial for people who had 3 previous lines of treatment. For progression-free survival, the interim subgroup analysis was based on only about half of patients having events. It showed that isatuximab plus pomalidomide and dexamethasone extended median progression-free survival compared with pomalidomide plus dexamethasone from 7.8 months to 13.3 months (hazard ratio 0.598; 95% confidence interval 0.348 to 1.03, p=0.0611). For time to death, the interim subgroup analysis was based on 11 deaths in the treatment group (which included 52 people) and 23 deaths in the control group (which included 58 people) and heavily censored data. It showed that median overall survival had not yet been reached for the isatuximab plus pomalidomide and dexamethasone arm. The hazard ratio for overall survival compared with pomalidomide plus dexamethasone was 0.494 (95% confidence interval 0.24 to 1.02, p=0.0502). The committee acknowledged the immaturity of the data in this ongoing trial. It concluded that isatuximab plus pomalidomide and dexamethasone was likely to extend progression-free and overall survival compared with pomalidomide plus dexamethasone after 3 previous lines of treatment, but noted that median follow up was short, the subgroup was small and the data were immature.

It is not appropriate to use isatuximab plus pomalidomide and dexamethasone when disease is refractory to a previous anti-CD38 monoclonal antibody

3.8 Isatuximab is an anti-CD38 monoclonal antibody. Daratumumab, another anti-CD38 monoclonal antibody, is an option after 1 previous line of treatment and 3 previous lines of treatments in the Cancer Drugs Fund. ICARIA-MM included people with multiple myeloma that was not refractory to anti-CD38 antibody treatment, that is, their disease had not progressed on the treatment. But, it excluded people whose disease was refractory to anti-CD38 antibody treatment, that is, their disease progressed while on the treatment. The clinical experts explained that they would consider using isatuximab plus pomalidomide and dexamethasone for people who had previous treatment with an anti-CD38 antibody such as daratumumab, but only if that treatment was stopped for reasons other than disease progression. They stated that they would not use an anti-CD38 antibody again if the disease had been refractory to one in a previous line of treatment. The company noted that only 1 person in ICARIA-MM had previous anti-CD38 antibody treatment. The clinical experts explained that in NHS practice many people increasingly have daratumumab after 1 previous line of treatment. This means that many people with relapsed and refractory multiple myeloma after 3 previous lines of treatment would have already had an anti-CD38 antibody. The Cancer Drugs Fund clinical lead noted that daratumumab is well tolerated and few people would stop it for reasons other than disease progression. The clinical experts and the Cancer Drugs Fund clinical lead also noted that there was high biological plausibility that response to isatuximab would be reduced in people whose disease was refractory to previous daratumumab treatment. The committee acknowledged that clinical-effectiveness evidence for isatuximab plus pomalidomide and dexamethasone in people who had previously had anti-CD38 antibody treatment had not been presented. It recalled that the clinical experts explained that using an anti-CD38 antibody treatment again later in the treatment pathway would be appropriate if it had been stopped for reasons other than disease progression. The committee concluded that it had not been presented with evidence for people whose disease was refractory to anti-CD38 antibody treatment. Also, it concluded that it was not appropriate to use isatuximab plus pomalidomide and dexamethasone when disease is refractory to a previous anti-CD38 monoclonal antibody.

Subsequent treatments in ICARIA-MM do not reflect NHS clinical practice

3.9 The subgroup of people in ICARIA-MM who had had 3 previous lines of treatment had a range of subsequent treatments after disease progression. The committee was aware that some of these treatments, such as daratumumab and lenalidomide, were not available at this point in the pathway in the NHS, and may prolong life. The clinical experts explained that for people who have had 4 previous lines of treatment, there are no standard treatments in current NHS clinical practice, and treatments at this point in the pathway would likely be ineffective. The clinical experts therefore considered that treatments after 4 or more previous lines of treatment in ICARIA-MM were unlikely to affect the survival results in the ICARIA-MM subgroup. At the second meeting, the Cancer Drugs Fund clinical lead noted that lenalidomide would likely be ineffective after 4 or more previous lines of treatment but daratumumab would give some benefit. The committee recognised that these treatment options improve clinical outcomes when used at other points in the treatment pathway, and it was appropriate to consider that they might also increase survival later in the treatment pathway. The committee also noted that the proportion of people having these treatments varied between arms in ICARIA-MM; more people had daratumumab in the pomalidomide plus dexamethasone arm and more people had lenalidomide in the isatuximab plus pomalidomide and dexamethasone arm. The committee concluded that the subsequent treatments people had in ICARIA-MM did not reflect NHS clinical practice. This made generalising the overall survival results from the trial to NHS practice problematic.

The company's economic model

The company's model is appropriate for decision making

3.10 The company chose a partitioned survival model to estimate the cost effectiveness of isatuximab plus pomalidomide and dexamethasone. The model included 3 health states: progression-free, progressed, and dead. The probability of being in a given health state was defined by the area under the curves for progression-free survival and overall survival or their difference. The model cycle

length was 1 week and the time horizon was 20 years. The committee considered the company's model to be appropriate for decision making.

Clinical experts prefer using a Weibull distribution to estimate overall survival in each trial arm

3.11 Follow up for the interim data from ICARIA-MM was short in relation to the modelled time horizon. So, the company extrapolated the overall survival data for the subgroup who had had 3 previous lines of treatment, choosing an exponential distribution in its base case. The committee understood that the distribution chosen to estimate overall survival affects the incremental cost-effectiveness ratio (ICER). The ERG noted that the exponential distribution provided the best statistical fit to the trial data, but other distributions had similar statistical fits. The committee noted that because there were limited trial data, the statistical fit of a curve is of limited importance when selecting the most appropriate distribution. It heard that 2 of the 3 clinical advisers to the company supported using the Weibull, whereas the other preferred the exponential distribution. The clinical experts at the first meeting also stated that the Weibull distribution produced the most plausible long-term estimates of overall survival in both trial arms. The committee noted that the overall survival estimates were uncertain because of the limited trial data and the clinical experts preferred the Weibull distribution to estimate overall survival in each arm.

The company updated its base case in response to consultation

3.12 At the second meeting, the company updated its base case to use a Weibull distribution to extrapolate the overall survival data for pomalidomide and dexamethasone from ICARIA-MM. It also provided supporting evidence for its original choice of an exponential distribution for estimating overall survival for isatuximab plus pomalidomide and dexamethasone. This evidence included no new survival data from ICARIA-MM, but it did include data documenting the experience of people who had daratumumab monotherapy after 4 previous lines of treatment (see section 3.13). The company also included an analysis using surrogate endpoints such as progression-free survival, depth of response to treatment and attaining minimal residual disease to model overall survival (see

section 3.14).

Clinical data are immature and there is a range of plausible distributions to estimate overall survival in each trial arm

3.13 To show potential overall survival beyond the ICARIA-MM trial follow-up period, the company identified a study that pooled overall survival for 2 single-arm trials of the anti-CD38 antibody daratumumab (GEN501 and SIRUS). The pooled data had a median follow up of 36.3 months compared with 11.6 months for the ICARIA-MM trial. The company stated that the exponential and log-normal distributions were the best fit for the longer-term daratumumab data. The ERG noted that it was reasonable to assume that treatments of the same class might follow a similar statistical model. The ERG explained that the hazard function (likelihood of dying) over time for the pooled daratumumab survival data appeared to decrease slightly. This suggested that using the Weibull distribution (which in this case is characterised by increasing hazards) was not appropriate to extrapolate the overall survival data for isatuximab plus pomalidomide and dexamethasone. The ERG preferred the exponential (constant hazards) to the Weibull distribution to estimate survival for isatuximab plus pomalidomide and dexamethasone because it did not consider that the hazard rate increased over time. The ERG also did an analysis using the log-normal distribution, which it considered plausible based on the current evidence because the log-normal function has decreasing hazards. The ERG stated it was reasonable to use a different distribution to extrapolate the overall survival data for isatuximab plus pomalidomide and dexamethasone to that used for pomalidomide and dexamethasone given that isatuximab has a different mechanism of action. But the ERG highlighted that when using separate distributions, it is not appropriate to apply a jointly fitted distribution as the company had done for the Weibull distribution to extrapolate the pomalidomide and dexamethasone data. Instead an independently fitted Weibull should be used. The committee noted that there was a range of plausible distributions to estimate overall survival in each trial arm. It concluded that the most appropriate hazard function to model overall survival for each treatment was uncertain because the clinical data are immature. But the exponential or the log-normal extrapolation for isatuximab plus pomalidomide and dexamethasone and the independently fitted Weibull for pomalidomide plus dexamethasone were plausible.

The company's alternative survival analysis using surrogates for overall survival is not robust

3.14 The company did an alternative survival analysis using other trial outcomes including minimal residual disease, depth of response to treatment, and progression-free survival data. It considered these outcomes to be surrogates for overall survival, because the ICARIA-MM data were immature. The company highlighted that more people had minimum residual disease and disease with a partial response or better with isatuximab plus pomalidomide and dexamethasone than with pomalidomide and dexamethasone. It suggested that those whose disease responded to treatment may live for a considerable length of time. The ERG acknowledged that survival may differ depending on whether there was minimal residual disease or response to treatment but these data from ICARIA-MM were uncertain. The company also did an analysis using an assumed ratio between progression-free and overall survival based on a literature search of meta-analyses of trials. The company identified 3 ratios that differed markedly and considered 1 of them to be the most plausible. The ratios were applied to the log-normal distribution it had used to estimate progression-free survival. This was then used to predict overall survival with the aim of validating the company's choice of the exponential distribution to model overall survival for isatuximab plus pomalidomide and dexamethasone. The company also did a separate analysis. This used overall survival data that the company had generated using progression-free survival data from ICARIA-MM and the ratio it considered most plausible to replace some of the censored overall survival data. The company noted that the overall survival outcomes based on the curves from these alternative analyses appeared to match those predicted by the company's preferred exponential distribution. The ERG highlighted that although progression-free survival correlated with overall survival, the exact relationship between these 2 parameters was uncertain and the company did not account for this. The committee was aware that progression-free survival is important to patients and is accepted by regulatory bodies as evidence of effectiveness, but is not a proxy for overall survival. The committee concluded that the analyses that used progression-free survival as a surrogate for overall survival were not robust. Also, they did not provide information on the most appropriate hazard function to extrapolate overall survival in people who had isatuximab plus pomalidomide and dexamethasone.

The company's log-normal extrapolation is appropriate to model progression-free survival

3.15 The company used a jointly fitted log-normal distribution to estimate progression-free survival in its base case. That is, it fitted a curve to data for both treatment arms and included treatment group as a covariate, implying a constant treatment effect over time. The company stated that the log-normal provided the best statistical fit to the data. The committee was aware that both the ERG and the company used other distributions in sensitivity analyses to estimate progression-free survival, but this had little effect on the economic model results. The committee agreed that the log-normal distribution was appropriate to estimate progression-free survival.

Adjusting trial data and costs for subsequent treatments is appropriate but the company did not provide the requested analysis

3.16 The committee was aware that some of the treatments given after 4 or more previous lines of treatment in ICARIA-MM would not be available in NHS clinical practice and might prolong life (see section 3.9). It was also aware that these subsequent treatments affected total costs in both treatment arms. For the committee's first meeting, the company used the inverse probability of censoring weighting method to adjust for the effect of treatment with daratumumab and lenalidomide after 4 previous lines of treatment. The company considered this analysis exploratory because it included a small number of people and may not have accounted for all the factors associated with subsequent daratumumab or lenalidomide use. The committee considered it reasonable to adjust for subsequent treatments in both arms of the trial, but noted that the company adjusted only 1 arm of the ICARIA-MM data. The committee was also not satisfied that the company had provided enough information about the analysis at the first meeting. At the second meeting, it noted that the company was unable to identify the covariates it had used. The committee could not evaluate the method of adjusting for subsequent treatments without knowing which covariates the company chose. The company stated that the analysis resulted in slightly increased survival estimates for both isatuximab plus pomalidomide and dexamethasone and pomalidomide and dexamethasone when daratumumab and

lenalidomide were removed. It considered this implausible and so did not present cost-effectiveness estimates using this adjustment. The committee concluded that adjusting the trial data and costs for subsequent treatments not available in clinical practice was appropriate, but the company did not fully report its methods or present results from the requested analysis.

It is reasonable to remove costs of daratumumab and lenalidomide, but this approach has limitations

3.17 The company's updated base case for the second committee meeting did not adjust for the effects or the costs of treatments given after 4 previous lines of treatment (see section 3.16). That is, the company considered that the overall survival results from a trial that used treatments unavailable in the NHS were generalisable to the NHS, and that the NHS would incur the costs of drugs it does not offer. The company explained that the clinical experts at the first committee meeting stated that these therapies were unlikely to affect survival after 4 or more previous lines of treatment. The ERG highlighted that this approach, that is, to maintain the effects but not remove the costs, was not appropriate. This was because it included high-cost treatments not recommended at this position in the treatment pathway in the NHS. The ERG noted that removing treatments reduced the total costs less in the isatuximab plus pomalidomide and dexamethasone arm than in the pomalidomide plus dexamethasone arm. This was because a higher proportion of people taking pomalidomide plus dexamethasone moved to daratumumab than did people taking isatuximab plus pomalidomide and dexamethasone. The committee recognised that the ERG's analysis that removed the costs of daratumumab and lenalidomide after 4 or more previous lines of treatment did not adjust for effects. The ERG noted that the reported survival hazard ratio from the adjustment analysis was not markedly different to that from the current ICARIA-MM data. The committee concluded that it would have preferred to have seen analyses adjusting for both effects and costs of daratumumab and lenalidomide given after 4 previous lines of treatment, with the methods fully reported. But without these analyses, it was reasonable to remove the costs of these treatments, particularly because the clinical experts suggested that treatments given after 4 previous lines of treatment would likely have minimal effects on survival.

Utility values in the economic model

Utility estimates in the company's model are appropriate

3.18 ICARIA-MM included the EQ-5D-5L health questionnaire to measure health-related quality of life. The company mapped the EQ-5D-5L data to the EQ-5D-3L to estimate mean utility for the pre-progressed and progressed disease health states. This is in line with NICE's guide to the methods of technology appraisal. The utility value used for the progression-free health state in the isatuximab plus pomalidomide and dexamethasone arm was slightly higher than for the pomalidomide plus dexamethasone arm (0.719 compared with 0.717). The company applied a utility value of 0.611 to both arms for the progressed disease state. More adverse events occurred in the isatuximab plus pomalidomide and dexamethasone arm. The company did not apply utility decrements for adverse events. It explained that health utility data were collected at the beginning of every treatment cycle (every 2 weeks) in the trial and it assumed that the EQ-5D would capture any loss in utility from adverse events. The ERG considered this to be reasonable. The patient expert stated that despite the higher rate of adverse events in the isatuximab plus pomalidomide and dexamethasone arm of the trial, fewer people stopped treatment because of adverse events than in the pomalidomide plus dexamethasone arm (7.8% compared with 17.2%). On balance, the committee concluded that the utility estimates used in the company's model were appropriate.

Costs in the economic model

Time on treatment determines cost of treatment, and the company's choice of extrapolation is reasonable

3.19 The committee understood that the cost of treatment was a key driver in the cost effectiveness of isatuximab plus pomalidomide and dexamethasone. It also appreciated that time on treatment and price largely determine the cost of treatment. The company collected time on treatment data in ICARIA-MM. The committee was aware that because the trial is ongoing, some people were on

treatment at the time of the interim analysis (27.6% in the pomalidomide plus dexamethasone arm and 45.1% in the isatuximab plus pomalidomide and dexamethasone arm). This added uncertainty to any extrapolation. The company chose an exponential model in its base case to estimate time on treatment. The ERG highlighted that alternative models increased the ICER. The committee considered that there was some uncertainty around the most plausible model to use to estimate time on treatment, but concluded that the company's choice was reasonable, given the available data.

Including drug wastage and treatment costs based on relative dose intensities in ICARIA-MM is appropriate

3.20 In its base case, the company assumed drug wastage for isatuximab in line with previous NICE technology appraisal guidance in multiple myeloma. But the company also stated that there was potential for vial sharing, which could reduce drug wastage. The ERG modelled a scenario without drug wastage to highlight the effect on the ICER, while noting this was unlikely in clinical practice. The Cancer Drugs Fund clinical lead confirmed that drug wastage was likely, particularly if treatments are not widely used. The ERG noted that the relative dose intensity, that is, the ratio of the given dose to the planned dose, of pomalidomide was lower in the isatuximab plus pomalidomide and dexamethasone arm than in the pomalidomide plus dexamethasone arm in ICARIA-MM. It modelled a scenario that assumed 100% relative dose intensities in both treatment arms to highlight the effect on the ICER. The company explained that the differences in the relative dose intensities of pomalidomide between trial arms resulted from the trial allowing dose reductions of pomalidomide, but only missed doses of isatuximab. The committee concluded that drug wastage occurs, and the company's base-case drug wastage and relative dose intensity assumptions were appropriate.

Removing pomalidomide and dexamethasone costs from the isatuximab plus pomalidomide and dexamethasone arm is not appropriate

3.21 The company stated that there were challenges in showing the cost effectiveness of isatuximab plus pomalidomide and dexamethasone because of the relatively high cost of pomalidomide. Pomalidomide is made by a different company, and is available with a confidential discount. The company acknowledged at the second meeting that this meant that it did not know the price of its own treatment combination, or the comparator, both of which include pomalidomide (and dexamethasone). The company noted that pomalidomide plus dexamethasone was a NICE recommended treatment option for multiple myeloma after 3 treatments and is part of standard of care. Therefore it proposed 2 alternative scenario analyses, which removed the cost of pomalidomide and dexamethasone from the isatuximab plus pomalidomide and dexamethasone arm when:

- those on pomalidomide plus dexamethasone are on treatment
- those on pomalidomide plus dexamethasone stop treatment.

The committee noted that NICE's guide to the methods of technology appraisal states that all relevant costs should be included in the analysis. It concluded that removing pomalidomide and dexamethasone costs from the isatuximab plus pomalidomide and dexamethasone arm was not appropriate.

Waning of treatment effect

An increasing relative treatment effect of isatuximab plus pomalidomide and dexamethasone over time is potentially plausible but uncertain

3.22 The company's original base case assumed that the relative survival benefit of isatuximab plus pomalidomide and dexamethasone, compared with pomalidomide plus dexamethasone, was maintained at the same level after

treatment stopped, for the rest of a person's life. This means that people who survive long term have a lower risk of death at any point in time if they took isatuximab plus pomalidomide and dexamethasone arm than if they took pomalidomide plus dexamethasone, even long after treatment stops. The company did not include the possibility that the effects of treatment wane over time, but instead tested for proportional hazards, which the trial data supported. However, the ERG noted that the proportional hazards assumption was supported only for the observed trial follow-up period, with no evidence for what happens after this. The clinical experts explained that it was plausible for isatuximab plus pomalidomide and dexamethasone to have some treatment benefit that continues after stopping treatment, although it may not be maintained at the same level for the rest of a person's life. The committee heard that the point at which the relative treatment benefit starts to diminish was unknown and how long the relative benefit lasts after stopping treatment was uncertain. At the second meeting, the company included in its updated base case an exponential distribution (constant hazard rate) to extrapolate overall survival data for isatuximab plus pomalidomide and dexamethasone. It also included a Weibull distribution (increasing hazard rate) to extrapolate overall survival for pomalidomide and dexamethasone (see section 3.12). The company stated that the exponential distribution likely included treatment effect waning because people whose disease responds to isatuximab plus pomalidomide and dexamethasone could be expected to live for a considerable length of time (see section 3.14). The ERG explained that by using an exponential distribution for isatuximab plus pomalidomide and dexamethasone, and a Weibull distribution for pomalidomide and dexamethasone, the relative treatment effect of isatuximab plus pomalidomide and dexamethasone increased over time. The ERG stated that this may be plausible because of the different mechanisms of action of the treatments but also based on the hazards seen in the daratumumab survival data (see section 3.13). The company did an analysis that included treatment effect waning by setting the hazard ratio associated with survival to 1.0 (no effect of treatment) at 3 years in the model, when approximately 90% of people had died. The company stated that this did not give plausible survival estimates for isatuximab plus pomalidomide and dexamethasone. This was because the estimated overall survival was shorter than for daratumumab monotherapy (see section 3.13), which the company considered should be inferior to triple combination therapy. The committee understood that this conclusion, based on an informal and naive comparison, would hold only if the people in ICARIA-MM

and the pooled daratumumab monotherapy trials were similar. The committee considered that an increasing relative treatment effect of isatuximab plus pomalidomide and dexamethasone over time was potentially plausible, but is highly uncertain because of the immaturity of the ICARIA-MM data.

End of life

Isatuximab plus pomalidomide and dexamethasone after 3 previous lines of treatment meets NICE's end-of-life criteria

3.23 The committee considered the advice about life-extending treatments for people with a short life expectancy in NICE's guide to the methods of technology appraisal. Median overall survival in the pomalidomide plus dexamethasone arm of the ICARIA-MM subgroup who had 3 previous lines of treatment was 14.4 months. The ERG noted that the modelled mean survival was higher than the median (these values are commercial in confidence and cannot be reported here). The company referred to epidemiological evidence showing that median overall survival was less than 14 months in people with relapsed or refractory multiple myeloma who had 3 previous lines of treatment. The clinical experts stated that life expectancy for people in this group was less than 2 years. Therefore, the committee concluded that the short life expectancy criterion was met. Median overall survival was not reached in the isatuximab plus pomalidomide and dexamethasone arm of ICARIA-MM. But both the Weibull (committee's preferred distribution) and the exponential model (company's base case) estimated that it extended life by more than 3 months compared with pomalidomide plus dexamethasone in people who had 3 previous lines of treatment. The committee acknowledged the uncertainty in the life-extending benefits of the treatment. But, on balance, it concluded that isatuximab plus pomalidomide and dexamethasone extended mean overall survival by over 3 months compared with pomalidomide plus dexamethasone. The committee concluded that isatuximab plus pomalidomide and dexamethasone, after 3 previous lines of treatment, met the criteria to be considered a life-extending, end-of-life treatment.

Cost-effectiveness results

The cost-effectiveness analysis after 2 previous lines of treatment is not robust enough for decision making

3.24 At the second meeting, the company did an analysis using data from people who had had 2 previous lines of treatment. It compared isatuximab plus pomalidomide and dexamethasone with panobinostat plus bortezomib and dexamethasone, the comparator listed in NICE's final scope after 2 previous lines of treatment. This was in response to the committee's request at the first meeting after hearing that there was unmet need at this part of the treatment pathway (see section 3.4). The company explained that it considered this analysis exploratory because the ICARIA-MM data were even less mature for people who had 2 previous lines of treatments than it was for people who had 3 previous lines of treatment. The company did not consider the indirect comparison to be robust and noted that panobinostat plus bortezomib and dexamethasone is not widely used in the NHS at this point in the treatment pathway. The committee agreed that there is unmet need for new effective treatment options for people who have had 2 previous lines of treatment, but concluded that the analysis of isatuximab plus pomalidomide and dexamethasone compared with panobinostat plus bortezomib and dexamethasone after 2 previous lines of treatment was not robust enough for decision making.

The committee states its preferred assumptions

3.25 Because of confidential commercial arrangements for isatuximab, pomalidomide and the comparators, none of the cost-effectiveness results are reported here. The committee recalled its preferred assumptions for analyses that:

- estimate overall survival using an exponential or log-normal extrapolation in the isatuximab plus pomalidomide and dexamethasone arm and an independently fitted Weibull extrapolation in the pomalidomide and dexamethasone arm (see section 3.13)
- use survival estimates for both treatment arms that are adjusted for daratumumab and lenalidomide, which are not used in NHS clinical practice

after 4 or more previous lines of treatment; with or without (depending on the validity of the adjustment analysis) removing the costs of these treatments (see section 3.9 and section 3.17)

- apply the drug wastage and relative dose intensity assumptions from the company's base case (see section 3.20).

Isatuximab plus pomalidomide and dexamethasone is not recommended for routine use in the NHS

3.26 The committee considered that the evidence base was immature, which meant that the most plausible ICER range was highly uncertain. The committee agreed that the uncertainty in the current evidence base was too high for it to be confident that the most plausible ICER range was below the range NICE normally considers to be a cost-effective use of NHS resources for a life-extending treatment at the end of life. It therefore concluded that it could not recommend isatuximab plus pomalidomide and dexamethasone for routine use in adults with relapsed and refractory multiple myeloma.

Cancer Drugs Fund

Isatuximab plus pomalidomide and dexamethasone meets the Cancer Drugs Fund criteria

3.27 Having concluded that isatuximab plus pomalidomide and dexamethasone could not be recommended for routine use, the committee then considered if it could be recommended for treating multiple myeloma within the Cancer Drugs Fund. The committee discussed the arrangements for the Cancer Drugs Fund agreed by NICE and NHS England in 2016, noting NICE's Cancer Drugs Fund methods guide (addendum). It recalled:

- The company expressed an interest in isatuximab plus pomalidomide and dexamethasone being considered for the Cancer Drugs Fund.

- Data from ICARIA-MM were immature (data cut was October 2018) and median overall survival was not reached in the isatuximab plus pomalidomide and dexamethasone arm.
- ICARIA-MM is due to finish in March 2022. Further data from this trial could help reduce uncertainties in estimating long-term progression-free and overall survival and the time on treatment. The committee was aware that overall survival and time on treatment estimates were key drivers of the cost-effectiveness results (see sections 3.11, 3.12, 3.13 and 3.19).
- Data collection through the Systemic Anti-Cancer Therapy dataset could be used to collect evidence on clinical outcomes for people with multiple myeloma who have had 3 previous lines of treatment. It may also provide information on the proportion of people having treatment after progression on 4 previous lines of treatment and the treatments used. However, there may not be enough time for these data to be collected before ICARIA-MM ends.
- The Cancer Drugs Fund clinical lead stated that because daratumumab, an anti-CD38 monoclonal antibody, is used after 1 previous line of treatment, there are fewer people eligible for isatuximab, another anti-CD38 monoclonal antibody treatment, after 3 previous lines of treatment. This may further limit the amount of data that would be collected for isatuximab in clinical practice.
- The company's price for isatuximab, including a commercial arrangement, means that it has plausible potential to be cost effective after 3 previous lines of treatment.

  The committee concluded that isatuximab plus pomalidomide and dexamethasone met the criteria to be considered for inclusion in the Cancer Drugs Fund, when the company's commercial offer as part of the managed access agreement is used. It recommended isatuximab plus pomalidomide and dexamethasone for use through the Cancer Drugs Fund as an option for relapsed and refractory multiple myeloma. It is only recommended if people have had 3 previous lines of treatment (including lenalidomide and a proteasome inhibitor), and their disease has progressed on the last treatment. Also, the conditions in the managed access agreement must be followed. When the guidance is next reviewed, the company should use the

committee's preferred assumptions (unless new evidence indicates otherwise), as set out in section 3.25.

Innovation

The model adequately captures the benefits of isatuximab plus pomalidomide and dexamethasone

3.28 The company considered isatuximab plus pomalidomide and dexamethasone to be innovative. This is because it is the first treatment option for relapsed and refractory multiple myeloma to combine an anti-CD38 monoclonal antibody and an immunomodulatory agent. The company also highlighted that the treatment shows benefit in a population who have had many previous lines of treatment. The Cancer Drugs Fund clinical lead stated that there are currently no anti-CD38 antibody treatments recommended for NHS routine commissioning to treat multiple myeloma. He also noted that the company supported a recommendation in the Cancer Drugs Fund. But the Cancer Drugs Fund already offers access to anti-CD38 antibody treatment after 1 previous line of treatment (daratumumab plus bortezomib and dexamethasone) and after 3 previous lines of treatment (daratumumab alone). At the second meeting, the company stated that although all relevant health benefits were captured in the model, there were likely to be other benefits that the model did not account for. These additional benefits included hope for people with multiple myeloma at later lines of treatment and improved quality of life for carers. The ERG noted the possibility that hope was captured by the anxiety and depression domain of the EQ-5D in the clinical trial and that the company did not investigate the impact on caregiver quality of life. The committee considered that the model captured all health-related quality-of-life benefits. It concluded that it had not been presented with any evidence of additional benefits from treatment with isatuximab plus pomalidomide and dexamethasone.

Other factors

3.29 No equality or social value judgement issues were identified.

4 Implementation

4.1 When NICE recommends a treatment as an option for use within the Cancer Drugs Fund, NHS England will make it available according to the conditions in the managed access agreement. This means that, if a patient has relapsed and refractory multiple myeloma and the doctor responsible for their care thinks that isatuximab plus pomalidomide and dexamethasone is the right treatment, it should be available for use, in line with NICE's recommendations and the Cancer Drugs Fund criteria in the managed access agreement. Further information can be found in NHS England's Appraisal and funding of cancer drugs from July 2016 (including the new Cancer Drugs Fund) – a new deal for patients, taxpayers and industry.

4.2 Chapter 2 of Appraisal and funding of cancer drugs from July 2016 (including the new Cancer Drugs Fund) – a new deal for patients, taxpayers and industry states that for those drugs with a draft recommendation for use in the Cancer Drugs Fund, interim funding will be available (from the overall Cancer Drugs Fund budget) from the point of marketing authorisation, or from release of positive draft guidance, whichever is later. Drugs that are recommended for use in the Cancer Drugs Fund will be funded in line with the terms of their managed access agreement, after the period of interim funding. The NHS England and NHS Improvement Cancer Drugs Fund list provides up-to-date information on all cancer treatments recommended by NICE since 2016. This includes whether they have received a marketing authorisation and been launched in the UK.

4.3 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance when the drug or treatment, or other technology, is approved for use within the Cancer Drugs Fund. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, for use within the Cancer Drugs Fund, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document or agreement of a managed access agreement by the NHS in Wales, whichever is the later.

5 Appraisal committee members and NICE project team

Appraisal committee members

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

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

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

NICE project team

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

Alan Moore
Technical lead

Emily Eaton Turner
Technical adviser

Jeremy Powell
Project manager

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