NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

Isatuximab in combination for untreated multiple myeloma when a stem cell transplant is unsuitable

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using isatuximab with bortezomib, lenalidomide 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: May 2025

Note that this document is not NICE's final guidance on isatuximab with bortezomib, lenalidomide 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- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using isatuximab with bortezomib, lenalidomide and dexamethasone in the NHS in England.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 comments: 19 June 2025
- Second evaluation committee meeting: 2 July 2025
- Details of the evaluation committee are given in section 4

1 Recommendations

1.1 Isatuximab plus bortezomib, lenalidomide and dexamethasone should not be used for untreated multiple myeloma in adults when an autologous stem cell transplant is unsuitable.

1.1 This recommendation is not intended to affect treatment with isatuximab plus bortezomib, lenalidomide 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

Isatuximab plus bortezomib, lenalidomide and dexamethasone is not required to be funded in the NHS in England for untreated multiple myeloma in adults when an autologous stem cell transplant is unsuitable. It should not be used routinely in the NHS in England.

This is because the available evidence does not suggest that isatuximab plus bortezomib, lenalidomide and dexamethasone is value for money in this population.

Why the committee made these recommendations

Usual treatment for untreated multiple myeloma when an autologous stem cell transplant is unsuitable is 1 of several combination treatments, most commonly daratumumab, lenalidomide and dexamethasone.

Clinical trial evidence suggests that, compared with bortezomib, lenalidomide and dexamethasone alone, adding isatuximab increases how long people live before their condition gets worse. But the bortezomib, lenalidomide and dexamethasone

combination is not used in the NHS. Also, the trial is ongoing so there is not enough evidence to tell whether adding isatuximab increases how long people live.

Isatuximab plus bortezomib, lenalidomide and dexamethasone has not been directly compared in a clinical trial with combinations used in the NHS, including daratumumab, lenalidomide and dexamethasone. The results of an indirect comparison suggest that it is likely to work as well as these combinations, but this is uncertain because of limitations in the analysis.

There are also uncertainties in the economic model, including the modelling of:

- time to stopping treatment
- how quality of life changes after treatment is stopped
- how long people with multiple myeloma live.

The cost-effectiveness estimates for isatuximab plus bortezomib, lenalidomide and dexamethasone are substantially higher than what NICE considers an acceptable use of NHS resources. So, it should not be used.

2 Information about isatuximab

Marketing authorisation indication

2.1 Isatuximab (Sarclisa, Sanofi) is indicated 'in combination with bortezomib, lenalidomide, and dexamethasone, for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant'.

Dosage in the marketing authorisation

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

Price

2.3 The list price of isatuximab is £506.94 per 100 mg/5 ml vial and £2,534.69 per 500 mg/25 ml vial (excluding VAT; BNF online accessed May 2025).

2.4 The company has a commercial arrangement. This makes isatuximab available to the NHS with a discount and it would have also applied to this indication if isatuximab had been recommended. The size of the discount is commercial in confidence.

Carbon Reduction Plan

2.5 Information on the Carbon Reduction Plan for UK carbon emissions for Sanofi will be included here when guidance is published.

3 Committee discussion

The evaluation committee considered evidence submitted by Sanofi, 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 an incurable, relapsing and remitting cancer of plasma cells. It is a chronic condition that affects how long people live and the quality of their lives. The patient experts emphasised that multiple myeloma is a highly individual and complex cancer that has a wide range of symptoms and varies in severity. They explained that the condition has a large psychological impact because of the constant possibility of relapse. With each relapse, the condition is more difficult to treat and the number of future treatment options becomes more limited. The patient experts added that the condition can also have a large impact on quality of life, affecting all aspects of life for people with the condition, and their family and carers. The committee acknowledged that multiple myeloma is a chronic, incurable highly individual condition that can have a negative impact on quality of life for people with the condition, and their families and carers.

Treatment pathway

3.2 First-line treatment options for people with multiple myeloma depend on whether a stem cell transplant may be suitable. NICE recommends the following treatments as options at first line when a stem cell transplant is not suitable:

- thalidomide, cyclophosphamide and dexamethasone (see NICE's technology appraisal guidance on bortezomib and thalidomide for the first-line treatment of multiple myeloma, from here TA228)
- bortezomib, cyclophosphamide and dexamethasone (Cyclo-Bor-Dex; see TA228)
- bortezomib, melphalan and prednisone (Mel-Bor-Pred; see TA228)
- lenalidomide and dexamethasone (Len-Dex; NICE's technology appraisal guidance on Len-Dex for previously untreated multiple myeloma, from here TA587)
- daratumumab, lenalidomide and dexamethasone (Dar-Len-Dex; see NICE's technology appraisal guidance on Dar-Len-Dex for untreated multiple myeloma when a stem cell transplant is unsuitable).

The clinical experts explained that multiple myeloma becomes resistant to treatment. This means the most effective treatment should be given as early as possible in the treatment pathway to achieve the deepest response and to prolong remission. The company explained that the thalidomide combination is very rarely used in the NHS. It added that Dar-Len-Dex is standard care for NHS patients with newly diagnosed multiple myeloma when an autologous stem cell transplant (ASCT) is unsuitable. The clinical experts explained that Dar-Len-Dex is the most relevant comparator. They added that people whose condition is not suitable for Dar-Len-Dex would not generally be offered isatuximab plus bortezomib, lenalidomide and dexamethasone (Isa-Bor-Len-Dex). But they highlighted that a few people who would currently have bortezomib-based regimens at first line for specific reasons such as renal failure may be offered Isa-Bor-Len-Dex instead. The NHS England Cancer Drugs Fund clinical lead explained that, each year in the NHS, 2,400 people have Dar-Len-Dex

and 300 people have Len-Dex. They also explained that NHS England does not collect data on the number of people who have bortezomib-based regimens. The committee noted that a few people are offered combination treatments other than Dar-Len-Dex in the NHS. But it concluded that Dar-Len-Dex was the most relevant comparator for Isa-Bor-Len-Dex.

Clinical evidence

Key clinical trial: IMROZ

3.3 The clinical-effectiveness evidence for Isa-Bor-Len-Dex came from IMROZ, a phase 3, multicentre, international, randomised, open-label, 2-arm, parallel-group study. It compared Isa-Bor-Len-Dex (n=265) with bortezomib, lenalidomide and dexamethasone (Bor-Len-Dex; n=181) in adults with newly diagnosed multiple myeloma when an ASCT was unsuitable. IMROZ had an initiation phase comprising 4 cycles of 6 weeks of treatment. This was followed by a maintenance phase of 4-week treatment cycles in which bortezomib was no longer used. In the maintenance phase, people randomised to the Bor-Len-Dex arm whose condition had progressed were allowed to crossover from Len-Dex to Isa-Len-Dex.

The primary endpoint was progression-free survival (PFS) as assessed by an independent review committee. The EAG noted that the company had presented results using data from the 26 September 2023 data cut, at which time median follow up was 59.7 months. It explained that this data could be considered somewhat immature. This was because median PFS had not been reached in the Isa-Bor-Len-Dex arm and median overall survival (OS) had not been reached in either trial arm. Clinical advice to the EAG was that people in IMROZ had similar demographic and disease characteristics to people seen in the NHS. So, the results of the trial were generalisable to NHS clinical practice. The committee noted that the average age of people in IMROZ was 71.6 years, which was younger than

would be expected for people in the NHS. One reason for this was because IMROZ excluded people who were over 80 years. The clinical experts explained that quadruplet combination treatments are usually only suitable for people who are fit enough to have them. They advised that a small proportion of people over 80 years would be considered fit enough to have Isa-Bor-Len-Dex. They added that only about 60% of people currently offered Dar-Len-Dex would be considered fit enough to have Isa-Bor-Len-Dex because of the additional treatment burden of quadruplet over triplet treatment combinations. The committee concluded that the IMROZ population was younger and fitter than the NHS population. But it agreed that the relative effects from IMROZ are likely to be generalisable to NHS clinical practice. It considered whether the data from IMROZ was sufficiently mature. It concluded that, while the data was immature and that this contributed to uncertainty in the survival analysis, the results of the trial were suitable for decision making.

Indirect treatment comparisons

3.4 The company explored different options for comparing Isa-Bor-Len-Dex with the relevant comparators: Dar-Len-Dex, Len-Dex, Cyclo-Bor-Dex and Mel-Bor-Pred. No randomised controlled trials were identified to support an indirect treatment comparison (ITC) compared with Cyclo-Bor-Dex. For this comparison, the company explained that it chose an inverse probability weighting (IPW) approach. This used patient-level data from IMROZ and from a retrospective, observational, cohort study done using data from the Flatiron Health Multiple Myeloma Enhanced DataMart. The EAG agreed that, in the absence of direct evidence, this choice of ITC for Cyclo-Bor-Dex was appropriate. For the remaining comparators, the company first considered a network meta-analysis (NMA) for the comparison with Dar-Len-Dex, Len-Dex and Mel-Bor-Pred. The company explained that it had included SWOG S0777 to allow network connectivity but this may have introduced substantial biases to the NMA. This was because outcome data was not reported specifically for the transplant-

ineligible subgroup relevant to this decision problem. Instead, it was categorised by:

- age ('under 65 years' compared with '65 years and over')
- intent to transplant ('yes' compared with 'no')
- whether there was a transplant ('yes' compared with 'no').

The company proposed that the subgroup of people aged 65 years and over was the most appropriate proxy for a transplant-ineligible subgroup analysis. But it explained that, because transplant eligibility is not solely defined by age, this subgroup may not fully have represented the transplant-ineligible population. Also, 18 out of 91 people in this subgroup had an intention to have a transplant, but the number who went on to have a transplant in this age group was unknown. Randomisation was also not preserved between treatment arms within this subgroup because the trial was not stratified by age. This led to potential imbalances in patient characteristics between treatment arms, biasing the estimate of relative treatment effects. Lastly, the company explained that in SWOG S0777, bortezomib was administered intravenously rather than subcutaneously. This caused a large proportion (23%) of people to prematurely stop Cyclo-Bor-Dex induction treatment because of neuropathy. This meant that the survival outcomes for the Cyclo-Bor-Dex arm may have been underestimated and confounded by early treatment discontinuation.

The EAG agreed with the company that the NMA results were unlikely to be robust because of the inclusion of the non-randomised subgroup from SWOG S0777 data. So, the company explained that it instead chose to use an unanchored matching-adjusted indirect comparison (MAIC). The EAG noted that unanchored MAICs rely on strong assumptions that are difficult to satisfy. This includes the assumption that all potential prognostic factors and treatment-effect modifiers are accounted for and included in the model. It explained that bias from unmeasured

confounding may have been introduced. It also explained that it was not possible to adjust for 3 out of 9 of the identified prognostic factors or treatment-effect modifiers (chromosomal abnormality 1q21+, serum lactate dehydrogenase [LDH] levels, frailty). The clinical experts advised that, of these, only frailty was potentially of concern because it is closely related to age. They added that this is an important prognostic variable and also determines potential eligibility for Isa-Bor-Len-Dex and Dar-Len-Dex. The company explained that frailty is usually a composite measure involving variables such as age and Eastern Cooperative Oncology Group Performance Status (ECOG PS). It said that that it had already adjusted for these in the analysis. The clinical experts agreed that these were components of frailty, but that frailty was much broader and included several other variables such as comorbidities.

The committee considered the relative merits of both ITC approaches. It noted that it would prefer to use randomised evidence when available. It agreed that there was not enough justification to discount the possibility of using results from the NMA with the inclusion of SWOG S0777. It noted that the relative effect from SWOG S0777 was likely to be applicable to the transplant-ineligible population. The committee suggested to the company that it could be possible to preserve randomisation by using the no intent-to-transplant subgroup as a proxy for when an ASCT is unsuitable. The company responded that its decision to discount this possibility had been informed by clinical expert opinion. The clinical experts explained that intent to transplant is not the same as having an ASCT. This is because intent is not always based on fitness. So, it is not the same as transplant suitability because the intention may change over time after the initial clinical assessment. The EAG noted that an unanchored MAIC is less robust than an NMA. But it explained that the limitations of the MAIC were known, whereas the risk and direction of bias in the company's NMA were unknown. The committee expressed its concern that use of the NMA results was not considered. It was

particularly concerned about whether it was possible to preserve randomisation using the no intent-to-transplant subgroup as a proxy, which would result in a conservative estimate. The committee noted that randomisation was stratified based on intent to transplant. The committee concluded that it would like the company to present results from an NMA using the SWOG S0777 study with randomisation preserved. It added that this should be done using both the intention-to-treat (ITT) population and the no intent-to-transplant subgroup as a proxy for the transplant-ineligible population. It concluded that these results should be used to inform the cost-effectiveness estimates.

Clinical-effectiveness results

3.5 For the ITT population, death or disease progression occurred in 84 (31.7%) of people in the Isa-Bor-Len-Dex arm and 78 (43.1%) in the Bor-Len-Dex arm. Median follow up was 59.70 months. The hazard ratio was 0.596 (98.5% confidence interval [CI] 0.406 to 0.876; p=0.0005). This corresponded to a 40.4% reduction in the risk of disease progression or death with Isa-Bor-Len-Dex compared with Bor-Len-Dex. The median PFS was not reached (NR) in the Isa-Bor-Len-Dex group and was 54.34 months (95% CI 45.207 to NR) in the Bor-Len-Dex group. OS was a secondary endpoint. At median follow up, 69 (26.0%) of people had died in the Isa-Bor-Len-Dex arm and 59 (32.6%) had died in Bor-Len-Dex arm. The hazard ratio for OS for Isa-Bor-Len-Dex compared with Bor-Len-Dex was 0.776 (99.97% CI 0.407 to 1.480; p=0.0760). Results from the unanchored MAICs and the NMA for Dar-Len-Dex and Len-Dex are considered commercial in confidence by the company and cannot be reported here. For Mel-Bor-Pred, the hazard ratio for the comparison with Isa-Bor-Len-Dex for PFS was 0.20 (95% CI; 0.15 to 0.27) and for OS was 0.50 (95% CI; 0.37 to 0.67). For Cyclo-Bor-Dex, the hazard ratio for the comparison with Isa-Bor-Len-Dex for PFS was 0.34 (95% CI; 0.25 to 0.47) and for OS was 0.48 (95% CI; 0.33 to 0.69).

Economic model

Company's modelling approach

3.6 The company provided a partitioned survival model to estimate the cost effectiveness of Isa-Bor-Len-Dex compared with Dar-Len-Dex and the other comparator combinations. The model included 3 health states: progression free (with subhealth states for on and off treatment), progressed disease and death. The probability of being in each health state was calculated using extrapolated PFS and OS curves. The model used a cycle length of 2 weeks with a half-cycle correction over a lifetime horizon of 29 years (the starting age in the model was 71.6 years). The OS rate was capped by the age and gender-matched general population mortality rate. Everyone was assumed to be dead at age 100 years. In each cycle, the PFS rate was capped by the OS rate for the same time period to ensure that OS was always greater than PFS. The committee concluded that, overall, the company's model structure was acceptable for decision making. But it noted that the multiple myeloma treatment pathway is becoming increasingly complex and with increasing lines of treatment available. So, it noted that having a single progressed-disease health state was a simplification and may not fully reflect the current treatment pathway and quality of life in this health state. It also recalled that the starting age used in the model, based on the age in IMROZ, was younger than would be expected in NHS clinical practice (see section 3.3). So, it requested that the model be updated to include a starting age reflecting the NHS population and based on an appropriate source. Its preference was people having Dar-Len-Dex in Systemic Anti-Cancer Therapy (SACT) data.

Modelling PFS and OS

3.7 In its base case, the company modelled differences in PFS and OS between treatments based on extrapolated data from IMROZ Kaplan–Meier curves and the ITCs. The company jointly fitted distributions to MAIC-adjusted IMROZ data (Isa-Bor-Len-Dex) and comparator (Dar-Len-

Dex, Mel-Bor-Pred and Len-Dex) trial OS and PFS Kaplan–Meier data. For Cyclo-Bor-Dex, the company also jointly fitted distributions to IMROZ ITT data for Isa-Bor-Len-Dex and the IPW-adjusted OS and PFS data for Cyclo-Bor-Dex. The company then estimated time-varying hazard ratios by comparing intervention and comparator survival estimates at different time points. These hazard ratios were applied to IMROZ ITT population OS and PFS distributions to generate survival estimates for people having Dar-Len-Dex, Mel-Bor-Pred, Len-Dex and Cyclo-Bor-Dex. The company considered that the most appropriate distributions to generate long-term survival estimates were the Gompertz distribution for OS and the Gamma distribution for PFS. The EAG explained its view that the company's approach was overly complicated. It thought that the fitted distributions used to estimate time-varying hazard ratios could have been used directly in the company's model. It further explained that, at all time points, survival estimates based on IMROZ MAIC-adjusted OS and PFS data were lower than the survival estimates based on IMROZ ITT data. So, generating survival estimates based on IMROZ Isa-Bor-Len-Dex ITT Kaplan–Meier data generated optimistic OS estimates for Isa-Bor-Len-Dex. The EAG also noted that the company had fitted distributions to the full 68 months of available IMROZ data but that, after 60 months, the only events remaining were censoring events. The company agreed with the EAG that most events past 60 months were censoring events. But it explained that limiting analysis to 60 months did not take into account all the available evidence. This was particularly true in the case of the MAIA trial (Dar-Len-Dex compared with Len-Dex in people with newly diagnosed multiple myeloma in whom an ASCT is unsuitable). Survival data from this trial was available for up to 100 months of follow up.

The company further explained that conventional extrapolation techniques apply less emphasis to the tail of data when there are fewer people at risk. Censoring people after 60 months for Isa-Bor-Len-Dex only marginally changed the survival estimates for OS and PFS. This suggested that the

tail did not introduce statistically significant uncertainty. The EAG disagreed with the company's preference for including data beyond 60 months, and noted that including this data also contributed to overly optimistic OS estimates for Isa-Bor-Len-Dex. So, at the clarification stage, it asked the company to provide analysis in which distributions were fitted only to the first 60 months of data. The company provided 2 new analyses in response to the EAG's request. Scenario A was limited to 60 months of data from the IMROZ and MAIA, and was the analysis preferred by the EAG. Scenario B used the full 68-month follow up of IMROZ and also included additional follow up from MAIA up to 100 months. But the company did not do as the EAG had requested. This was to fit separate distributions to the first 60 months of MAIC-adjusted IMROZ Isa-Bor-Len-Dex data and comparator trial data and use these distributions directly in the economic model. Instead, the company maintained its original approach, but using the 60-month data. The clinical experts explained that the high proportion of censoring events after 60 months in IMROZ added uncertainty to the survival analysis. They added that it is often preferable to use as much clinical trial data as is available. But they thought it was reasonable to exclude IMROZ data after 60 months from the analysis.

After the EAG's request at the clarification stage for new analyses up to 60 months, the company revised its selection of parametric curves for Isa-Bor-Len-Dex. It preferred using Weibull for PFS and generalised gamma for OS. For PFS, the EAG explained that it thought that the Gompertz distribution was a better choice than Weibull. This was because it was similarly ranked and generated estimates that were more closely aligned to clinical expert opinion. For OS, the EAG noted that the Gompertz distribution was a better fit based on Akaike information criterion and Bayesian information criterion statistics. It also generated OS estimates that were closer to clinician landmark estimates. The clinical experts noted that, because of the age of people at diagnosis, it was very difficult to validate estimates of PFS and OS. This was particularly difficult out to a

20-year timepoint in which the model extrapolations were all overoptimistic. But, despite this caveat, the clinical experts thought that the clinical expert opinion provided by the company was reasonable. They also preferred the EAG's chosen distributions because of their closer alignment with these clinician landmark estimates. The EAG explained that the choice of extrapolation had a relatively small impact on cost effectiveness. This was particularly so when compared with the choice of whether to use the 60-month or 68-month analysis.

The committee agreed with the EAG that the company's approach was overly complicated, and that the calculation of time-varying hazard ratios was an unnecessary step. The committee noted that the company's and EAG's approach to modelling OS and PFS was highly uncertain because it relied on the results from the unanchored MAIC. It recalled that it would have preferred to see ITC results from an NMA that maintained randomisation (see section 3.4). So, it was unable to conclude on the most appropriate OS and PFS parametric distribution, and whether 60 or 68 months of data should be used. The committee concluded that its preferred method to model OS and PFS for Isa-Bor-Len-Dex and comparators would be to apply the hazard ratio generated from an NMA to an appropriate reference curve, such as Dar-Len-Dex OS and PFS curves from MAIA or Dar-Len-Dex SACT data.

OS benefit

3.8 The company explained that the MAIC results suggested an OS benefit for Isa-Bor-Len-Dex compared with Dar-Len-Dex because the hazard ratio was less than 1. Based on Kaplan–Meier curves, the mortality rates for Isa-Bor-Len-Dex and Dar-Len-Dex were:

- equal for the first 12 months
- possibly higher for Dar-Len-Dex between months 12 and 24
- possibly higher for Isa-Bor-Len-Dex between months 24 and 36, becoming equal again from month 36 onwards.

The EAG noted that the available clinical-effectiveness evidence was not sufficient to support the assumption that people having Isa-Bor-Len-Dex live longer than people having Dar-Len-Dex. It also noted that this apparent fluctuation in mortality rates over time may have been a statistical artefact. This was because the OS hazard ratios presented by the company for this comparison were close to 1 and not statistically significantly different from 1. The company explained its view that the increase in mortality for people having Isa-Bor-Len-Dex could be attributed to the 12 COVID-19-related deaths in IMROZ. No COVID-19-related deaths were recorded in MAIA because it was done before the pandemic. Had these COVID-19-related deaths not occurred in IMROZ, it would have expected the survival of Isa-Bor-Len-Dex to have remained above the Dar-Len-Dex OS curve. But the EAG noted that it was not correct to assume that these deaths were caused by COVID-19. This was because only a positive COVID-19 test had been recorded on the death certificates. It was unknown whether COVID-19 was the cause of death. The EAG also noted that the number of deaths associated with a positive COVID-19 test in IMROZ was low (n=12). So, it seemed unlikely that this fully explained the fluctuations. It also did not explain why mortality hazards from month 36 onwards appeared essentially identical for people having Isa-Bor-Len-Dex and people having Dar-Len-Dex. The EAG further noted that the survival differences appeared to be small. Despite this, the company's life year gain estimates accounted for about 30% of the total quality-adjusted life year (QALY) gain for Isa-Bor-Len-Dex compared with Dar-Len-Dex. The EAG explained that these inconsistencies and uncertainties in the OS data suggested that it was unclear that people having Isa-Bor-Len-Dex live longer than people having Dar-Len-Dex. So, it preferred to set OS as equal between the 2 treatments. The committee agreed with the EAG that it had not yet seen sufficient clinical evidence to support an OS benefit for Isa-Bor-Len-Dex compared with Dar-Len-Dex.

Modelling of time to treatment discontinuation and subsequent treatment costs

3.9 To estimate the proportion of people having subsequent treatments, the company used IMROZ data after Isa-Bor-Len-Dex and MAIA data after Dar-Len-Dex. It modelled PFS to be substantially longer for people having Isa-Bor-Len-Dex compared with people having Dar-Len-Dex. But it also modelled time to treatment discontinuation (TTD) for Isa-Bor-Len-Dex to be shorter than for Dar-Len-Dex. This resulted in a large difference between PFS and TTD for Isa-Bor-Len-Dex but no substantial difference between PFS and TTD for Dar-Len-Dex. The durations are considered commercial in confidence by the company and cannot be reported here. The EAG noted that both treatments are used until progression and the model assumed that the adverse events profile of Dar-Len-Dex is less favourable than that of Isa-Bor-Len-Dex. So, the EAG would have expected TTD for Isa-Bor-Len-Dex to be longer than for Dar-Len-Dex. It explained that this had an impact on subsequent treatment usage and costs in the model. This was because it was assumed that some people stop treatment with Isa-Bor-Len-Dex but do not have any further treatment until progression. The clinical experts confirmed that some people may stop treatment because of reasons such as toxicity or a desire to avoid repeated hospital visits. They also confirmed that some people may have a deep and lasting response to Isa-Bor-Len-Dex even after treatment has stopped. The EAG noted that IMROZ had a shorter follow up than MAIA, so there was less time for people who had progressed to start a subsequent treatment. It suggested that the total cost associated with Isa-Bor-Len-Dex could have been underestimated in the company's economic model if:

- the difference between PFS and TTD modelled for Isa-Bor-Len-Dex is not reflected in NHS practice
- people who stop treatment with Isa-Bor-Len-Dex have subsequent treatments before progression.

The committee concluded that the TTD and PFS values used by the company were uncertain and may not reflect NHS practice. It also recalled

there may be an additional treatment burden of quadruplet over triplet treatment combinations (see section 3.3). So, it would not expect Dar-Len-Dex to have a worse adverse events profile than Isa-Bor-Len-Dex. It requested that the company provide further justification for why:

- there is such a large difference between TTD and PFS for Isa-Bor-Len-Dex
- there is such a small difference between TTD and PFS for Dar-Len-Dex
- TTD was shorter for Isa-Bor-Len-Dex than for Dar-Len-Dex.

Health-state utility values

3.10 The company did not use the post-progression health-state utility value from IMROZ to inform the economic model. The utility value is considered commercial in confidence by the company, so cannot be reported here. The company thought that the utility value was overly optimistic because health-related quality-of-life records were clustered after progression events. So, it did not fully take account of the full post-progression period. The company also explained that the utility value only accounted for second-line treatment. But it should have accounted for multiple relapses up to fourth line in the economic model. The company also explained its view that this utility value was not sufficiently robust because it was derived from relatively few people. For these reasons the company explained that it preferred to use the post-progression utility value of 0.557 from TA587 (that is, Len-Dex for untreated multiple myeloma). But the EAG noted that the post-progression utility value in IMROZ was based on data from 97 people. It thought this was a large enough sample for the utility value to be robust. It also explained that the PFS utility value from TA587 was low compared with the PFS utility value from IMROZ. So, it follows that the post-progression utility value from TA587 was also potentially too low. The EAG further noted that TA587 was done 12 years ago, and that there were now many more effective treatments available. It explained that the company's economic model was too simplistic to account for utility values falling as people progressed through multiple

relapses and subsequent lines of treatment. The EAG also explained that the oversimplification of assuming that everyone would have a post-progression utility value as low as that at the time of TA587 was not clinically plausible. It preferred to use the IMROZ post-progression utility value in the model. The clinical experts agreed that the post-progression utility value should capture health-related quality of life over the course of multiple lines of treatment. So, they thought that it would have been preferable to look at more recent trials that were more representative of treatments used in the NHS. The committee noted that the company had included utility values from the study by Hatswell et al. (2019) as a scenario in the model. The committee agreed that the post-progression utility value from TA587 was low. This was because, at the time of that evaluation, fewer treatment options were available post-progression, which is not reflective of the current treatment pathway. So, the committee concluded that it was not appropriate to use utility values from TA587. It would prefer to use post-progression utility values from IMROZ, or treatment-independent progressed-disease utility values derived by applying a decrement based on Hatswell et al. to the IMROZ PFS utility value.

Cost-effectiveness estimates

Acceptable ICER

3.11 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. Because of confidential commercial prices for isatuximab, bortezomib and some comparator treatments, the ICERs are

confidential and cannot be reported here. The committee noted the high level of uncertainty, specifically:

- the robustness of the company's ITCs (see section 3.4)
- insufficient clinical evidence for an OS benefit for Isa-Bor-Len-Dex compared with Dar-Len-Dex (see section 3.8)
- inconsistencies in the modelling of TTD and subsequent treatment costs between Isa-Bor-Len-Dex and Dar-Len-Dex (see section 3.9)
- the appropriateness of the company's choice of utility value for the post-progression health state (see section 3.10).

So, the committee concluded that an acceptable ICER would be towards the lower end of the range NICE considers a cost-effective use of NHS resources (£20,000 to £30,000 per QALY gained).

Committee's preferred assumptions

3.12 The committee considered that neither the company's nor the EAG's base case included all its preferred assumptions, which were that:

- the economic model be informed by an NMA using SWOG S0777 with randomisation preserved using the ITT population and the no intent-to-transplant subgroup as a proxy for the transplant-ineligible population (see section 3.4)
- the economic model be updated to include a starting age that reflects the NHS population and based on an appropriate source, preferably SACT (see section 3.6)
- OS and PFS for Isa-Bor-Len-Dex and comparators be modelled by applying the hazard ratio generated from the revised NMA to an appropriate reference curve (see section 3.7)
- the economic model use post-progression utility values from IMROZ or values from Hatswell et al (2019; see section 3.10).

Areas needing clarification

3.13 The committee considered that there were many areas of uncertainty (see section 3.11) and would like to see clarification on whether:

- it is feasible to do an NMA using SWOG S0777 with randomisation preserved using the no intent-to-transplant subgroup as a proxy for the transplant-ineligible population (see section 3.4)
- there is further clinical evidence and a more robust justification to support the claim of an OS benefit for Isa-Bor-Len-Dex compared with Dar-Len-Dex (see section 3.8)
- the inconsistencies in the modelling of TTD and PFS are clinically justified and would be expected in NHS practice (see section 3.9).

Company and EAG cost-effectiveness estimates

3.14 The committee considered the cost effectiveness of Isa-Bor-Len-Dex compared with Dar-Len-Dex and the other relevant comparators. It noted that all the deterministic and probabilistic ICERs were substantially above £30,000 per QALY gained. The exact ICERs cannot be reported here because some prices are confidential.

Other factors

Equality

3.15 The committee did not identify any equality issues.

Conclusion

Recommendation

3.16 All the ICERs in the company's and EAG's analyses were substantially higher than the range considered to be a cost-effective use of NHS resources. So, Isa-Bor-Len-Dex should not be used for routine commissioning in the NHS for treating newly diagnosed multiple myeloma in adults when a stem cell transplant is unsuitable.

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 technology 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.

Luke Cowie

Technical lead

Nigel Gumbleton

Technical adviser

Vonda Murray

Project manager

Richard Diaz

Associate director

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