NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final draft guidance

Elranatamab for treating relapsed and refractory multiple myeloma after 3 or more treatments

1 Recommendations

1.1 Elranatamab is recommended with managed access as an option for treating relapsed and refractory multiple myeloma in adults, only after 3 or more lines of treatment (including an immunomodulatory drug, a proteasome inhibitor and an anti-CD38 antibody) when the multiple myeloma has progressed on the last treatment. It is only recommended if the conditions in the managed access agreement for elranatamab are followed.

1.2 This recommendation is not intended to affect treatment with elranatamab 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.

Why the committee made these recommendations

The main treatment that is used for multiple myeloma that has relapsed (come back) and is refractory (has stopped responding to treatment) after 3 or more lines of treatment is pomalidomide plus dexamethasone. If pomalidomide plus dexamethasone is not suitable, panobinostat plus bortezomib and dexamethasone can be used. If the multiple myeloma is refractory to 5 or more treatments, selinexor plus dexamethasone can be used. For this evaluation, the company only compared

Issue date: October 2024

elranatamab with treatments that are used after 3 or more lines of therapy. This does not include everyone who elranatamab is licensed for.

Elranatamab has not been directly compared in a clinical trial with pomalidomide plus dexamethasone, panobinostat plus bortezomib plus dexamethasone, or selinexor plus dexamethasone. Indirect comparisons with these treatments suggest that elranatamab could increase how long people have before their cancer gets worse. Indirect comparisons with pomalidomide plus dexamethasone and selinexor plus dexamethasone suggest that elranatamab could also increase how long people live. But elranatamab was not directly compared with any of these treatments and the clinical trial of elranatamab is still ongoing, so the long-term benefits are unknown.

To prevent or treat infections, people having elranatamab can have intravenous immunoglobulin, but it is uncertain how many people might have this in NHS clinical practice, and for how long. Because of this, and because of the uncertainty in the long-term benefits of elranatamab, the cost-effectiveness estimates are also uncertain.

Even when considering the condition's severity, and its effect on quality and length of life, the most likely cost-effectiveness estimates are above what NICE considers an acceptable use of NHS resources. So, elranatamab cannot be recommended for routine use in the NHS.

Elranatamab could be cost effective if further evidence shows that people live longer with this treatment. Longer-term evidence from the trial and NHS clinical practice could help address the remaining uncertainties. So, elranatamab is recommended for use with managed access only after 3 or more lines of treatment (including an immunomodulatory drug, a proteasome inhibitor and an anti-CD38 antibody) when the multiple myeloma has progressed on the last treatment.

2 Information about elranatamab

Marketing authorisation indication

2.1 Elranatamab (Elrexfio, Pfizer) is indicated 'as monotherapy for the treatment of adult patients with relapsed and refractory multiple myeloma, who have received at least three prior therapies, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody 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 elranatamab.

Price

2.3 The list price for elranatamab is £4,242.50 per 76 mg vial and £2,456.00 per 44 mg vial, (excluding VAT; BNF, accessed October 2024)

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

3 Committee discussion

The evaluation committee considered evidence submitted by Pfizer, 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

Details of condition

3.1 Multiple myeloma is an incurable and progressive condition that has a substantial impact on survival and quality of life. Complications of multiple myeloma can be significant, debilitating and painful. The relapsing–remitting nature of the condition has a huge psychological impact, as

people are aware that treatment options and life expectancy reduce with each relapse. Patient organisations said that there is a clear need for innovative treatments that deliver deep, durable responses for people with relapsed and refractory multiple myeloma. One patient expert explained that people with multiple myeloma are told early on that the condition comes back stronger with shorter remissions each time. The committee recognised the substantial impact multiple myeloma has on survival and quality of life. It acknowledged the unmet need for effective treatments for people with multiple myeloma who have already had several treatments.

Elranatamab

3.2 Elranatamab is a bispecific monoclonal antibody that binds to the B-cell maturation antigen on plasma cells, plasmablasts and multiple myeloma cells, as well as to the CD3 receptor on T-cells. Patient organisations highlighted that as elranatamab has a newer mechanism of action, it has the potential to overcome treatment resistance. One patient expert explained that there is hope that with elranatamab, people's relapsed and refractory multiple myeloma will be able to remain in remission for longer. Another patient expert added that there is also the psychological benefit of knowing another treatment option is available in case of relapse. Having flexibility of choice and being able to access a treatment when it's needed are important benefits for people with the condition. Patient experts reported that elranatamab does not have to be used in combination with steroids, unlike many other treatments for multiple myeloma, which is an advantage of this treatment. One patient expert explained that prolonged steroid treatment can be physically and mentally tough on people with multiple myeloma and their families. They also noted that elranatamab is given as a subcutaneous injection, which is more convenient than some other multiple myeloma treatments. This is because a subcutaneous injection avoids the need for lengthy and frequent hospital visits. This would be welcomed by people with multiple myeloma, their families and hospital staff. This is a distinct advantage of elranatamab compared with some other multiple myeloma treatments that are given as infusions. The

committee concluded that elranatamab is an innovative medicine, which could provide a novel treatment option for people with relapsed and refractory multiple myeloma.

Clinical management

Treatment pathway, positioning and comparators

3.3 According to the marketing authorisation, people having elranatamab must have had 3 or more treatments including an immunomodulatory drug, a proteasome inhibitor, and an anti-CD38 monoclonal antibody. The condition must have also progressed on the last treatment. The original company submission provided a comparison with pomalidomide plus dexamethasone (from now, POM+DEX). POM+DEX is a fourth line treatment. At the first committee meeting, the committee concluded that because of this, elranatamab could only be recommended after 3 or more lines of treatment, and only as an alternative to POM+DEX. In response to the draft guidance consultation, the company and patient groups explained that the draft recommendation restriction unfairly excluded people who could not have, or who had already had, treatment with POM+DEX. To support the restriction (only as an alternative to POM+DEX) being lifted, the company provided comparisons with panobinostat plus bortezomib plus dexamethasone (from now, PANO+BORT+DEX) and selinexor plus dexamethasone (from now, SEL+DEX). But the company said that PANO+BORT+DEX was an inappropriate comparator because it is not used a lot in the UK, and is often used as a drug of last resort because of its toxicity. It added that SEL+DEX was not initially considered as a comparator as it was not in the final NICE scope and has only recently been recommended by NICE (see NICE's technology appraisal guidance on SEL+DEX [TA970]). At the second committee meeting, the clinical experts agreed that only a small proportion of people with relapsed and refractory multiple myeloma would have PANO+BORT+DEX after 3 lines of treatment. The committee considered that the number of people having SEL+DEX would likely

increase following its positive recommendation for multiple myeloma that is refractory to 5 or more treatments. The committee discussed where in the treatment pathway elranatamab should be used and agreed with their previous conclusion that elranatamab should be considered at fourth line or later. The committee agreed that POM+DEX, PANO+BORT+DEX and SEL+DEX were comparators to elranatamab. The committee concluded that POM+DEX was the main comparator for this evaluation. It added that SEL+DEX may be used for people who have already had POM+DEX and that PANO+BORT+DEX would only be used for a small number of people. It added that the number of people having PANO+BORT+DEX would reduce over time because of newer drugs now entering the treatment pathway.

Clinical effectiveness

Elranatamab clinical trial data

3.4 The key clinical evidence for elranatamab in this indication came from MagnetisMM-3. This is a phase 2, non-randomised, open-label study in people with relapsed and refractory multiple myeloma that was refractory to at least 1 immunomodulatory drug, 1 proteasome inhibitor, and 1 anti-CD38 monoclonal antibody (triple-class refractory). The company presented data from cohort A of the study (n=123). This cohort included people who had not had prior B-cell maturation antigen (BCMA)-directed therapies such as antibody–drug conjugates or chimeric antigen receptor (CAR) T-cell therapies (that is, a BCMA-naive cohort). The company's original submission presented data from the 14 March 2023 data cut, with a median follow up of 15 months. The objective response rate based on an interim analysis of a subset of the cohort was 61%. Median overall survival (OS) and progression-free survival (PFS) were not reached at 15 months. In response to the draft guidance consultation, the company provided data from the 28-month data cut of MagnetisMM-3. In the updated data cut, median OS was 24.6 months (95% CI 13.4 to not estimable) and PFS was 17.2 months (95% CI 9.8 to not estimable). The

committee noted that because of elranatamab's novel mechanism of action, it had received its marketing authorisation sooner than usual and so was being evaluated by the committee earlier than usual. The committee concluded that the results from MagnetisMM-3 appeared promising, but agreed that the data was immature. This meant that there was substantial uncertainty around the clinical-effectiveness estimates. The committee then considered the generalisability of MagnetisMM-3 to people expected to have elranatamab in UK clinical practice. It noted that everyone in MagnetisMM-3 had triple-class refractory disease. During the first committee meeting, the clinical experts said that they expected that many people treated at fourth line in clinical practice would have triple-class refractory disease. But they said that for a few people, their disease may be triple-class exposed and refractory to the last treatment only. The committee concluded that the results of MagnetisMM-3 may not be generalisable to people whose disease was triple-class exposed but not triple-class refractory, but it noted that this was likely to be only a small number of people.

Comparison of elranatamab with POM+DEX

3.5 The clinical evidence for POM+DEX came from MM-003 (data cut-off March 2013). This was a phase 3, multicentre, randomised, open-label trial. People were eligible if they had been diagnosed with refractory or relapsed and refractory multiple myeloma, and had at least 2 previous treatment cycles of bortezomib and lenalidomide, alone or in combination (Miguel et al. 2013). The study compared pomalidomide plus low-dose dexamethasone (n=302) with high-dose dexamethasone (n=153). The objective response rate was 31.0%. Median OS was 11.9 months (95% confidence interval [CI] 10.4 to 15.5) and median PFS was 4.0 months (95% CI 3.6 to 4.7). As MagnetisMM-3 did not include a control arm, the company did an unanchored matching-adjusted indirect comparison (MAIC) to indirectly compare the elranatamab data from MagnetisMM-3 to data from the POM+DEX arm of MM-003. Hazard ratios for the unanchored MAIC were 0.386 (95% CI 0.253 to 0.589) for PFS and 0.705

(95% CI 0.494 to 1.007) for OS. The EAG noted that there were differences in the patient populations between the 2 trials, and the matching method significantly reduced the effective sample size. So, the results of the unanchored MAIC should be interpreted with caution. The committee considered the evidence presented for both treatments. It noted that MM-003 took place around 10 years before MagnetisMM-3, so it likely did not represent current clinical practice. The committee considered it unusual for a multiple myeloma trial not to include a control arm. The committee concluded that the lack of data from a randomised-controlled trial meant that the comparative effectiveness estimates were uncertain. In response to the draft guidance consultation, the company did unanchored MAICs to compare elranatamab with PANO+BORT+DEX and SEL+DEX. These are discussed, along with the modelling assumptions, in sections 3.10 and 3.11.

Economic model

Company's modelling approach

3.6 The company used a partitioned survival model with 4 health states:

- progression-free (on treatment)
- progression-free (off treatment)
- progressed
- death.

The cycle length was 1 week and the time horizon was 25 years. To partition the cohort across the model health states, the company used trial OS, PFS and time-to-treatment-discontinuation (TTD) data. The EAG was broadly satisfied with the company's model structure but had reservations about several assumptions and parameter selections used to determine health-state occupancy (see sections 3.7 to 3.11). The committee noted that the company's model was similar to previous models used for multiple myeloma and concluded that the model structure was appropriate for decision making.

PFS and OS extrapolations for elranatamab – comparison with POM+DEX

3.7 To estimate long-term PFS and OS in the comparison with POM+DEX, the company fitted parametric distributions to the digitised Kaplan–Meier data from MM-003 for POM+DEX, and to the MAIC-weighted Kaplan–Meier data from MagnetisMM-3 for elranatamab. The company preferred independently fitted parametric curves to using hazard ratios from the unanchored MAIC. This was because the company rejected the proportional hazards assumption based on the log cumulative hazards plots and Schoenfeld residual plots. The company selected the generalised gamma distribution for modelling both PFS and OS. The company's PFS and OS distributions crossed early in the extrapolation period. To overcome this, the company gave priority to the PFS curve, allowing the OS curve to converge with the PFS curve. The EAG explained that the company's preferred modelling approach resulted in a single curve being used to partition the cohort between the progression-free and death states from early in the model time horizon. This meant that after this point people had no risk of progression and only pre-progression mortality. The EAG added that this underestimated the time spent with progressed disease, underestimated subsequent treatment costs, and overestimated quality-adjusted life year (QALY) gains. The EAG presented an alternative approach using the same generalised gamma distribution for OS as the company but using the gamma distribution for PFS. Using this approach meant that the PFS and OS curves did not converge, maintaining a proportion of people in the post-progression health state over time. The EAG also provided a scenario that used the unanchored MAIC hazard ratios applied to the POM+DEX curves to estimate PFS and OS for elranatamab.

The clinical experts at the committee meeting acknowledged the uncertainty in predicting survival outcomes for elranatamab because of the immaturity of the data. One clinical expert explained that the condition

generally responds to new classes of drugs better than drugs that have been used previously. They added that there was good reason to be optimistic about elranatamab based on its newer mechanism of action. Because of this, they would expect PFS for elranatamab to be above the EAG's chosen gamma distribution, but they noted that the company's generalised gamma distribution was too optimistic. The committee agreed that it was difficult to predict long-term survival outcomes for elranatamab with any certainty based on the initial 15-month follow-up data provided at the first committee meeting. The committee considered the company's base-case approach and agreed that assuming only pre-progression mortality and no post-progression health state did not have face validity. It noted that the EAG's base-case extrapolations had better face validity because they resulted in a separate post-progression state. The committee noted the clinical expert's view that the EAG's preferred gamma distribution for PFS may be slightly pessimistic. But it considered that the EAG's approach avoided the issue of crossing PFS and OS curves. The committee recalled that further data from the MagnetisMM-3 study was now available, but felt that the limited amount of further data was unlikely to significantly reduce the uncertainty. The committee also discussed several additional modelling scenarios that may have helped to explore the uncertainty, such as:

- using the generalised gamma distribution to model OS and applying a hazard ratio based on observed MagnetisMM-3 data to the OS curve to estimate PFS
- using a hybrid modelling approach, with separate distributions fitted to PFS and OS curves for the observed period with the unanchored MAIC hazard ratios applied from the end of follow up
- modelling the average of the generalised gamma (optimistic) and exponential (pessimistic) distributions for OS.

The committee concluded that long-term PFS and OS were uncertain

given the immaturity of the data, but the EAG's base-case extrapolations were the most plausible of the options presented.

SMR adjustment – comparison with POM+DEX

3.8 The company adjusted its PFS and OS extrapolations for excess mortality. This was done by ensuring extrapolated hazards did not fall below an elevated all-cause mortality rate for people with multiple myeloma. The elevated mortality rate was calculated by applying standardised mortality ratios (SMRs) to UK age- and sex-matched general population mortality data. The company's SMRs were derived from the Giri et al. (2021) study in people who had survived for 2 years after autologous peripheral blood stem cell transplantation. The study reported overall and time-varying SMRs. The company's base case used time-varying SMRs. These were 15.3 in the first 5 years, 3.5 in years 6 to 10 and 1.0 after 10 years. The EAG highlighted that the cohort studied in Giri et al. was not aligned with the population that will have elranatamab in clinical practice, so the derived SMRs may not be applicable. It noted that people eligible for elranatamab will have multiple myeloma that has progressed after several lines of treatment. It was unclear whether this was the case for people in the Giri et al. study. The EAG also noted that not all people eligible for elranatamab will have had an initial transplant. The EAG cautioned that applying an SMR of 1.0 after 10 years implies that a proportion of the eligible population will have the same mortality as the general population. This would not be appropriate for a population of people with relapsed and refractory multiple myeloma who have already had several lines of treatment.

The EAG presented an alternative, illustrative scenario using an SMR of 1.2 after 10 years. One clinical expert at the committee meeting explained that survival for people with relapsed and refractory multiple myeloma has improved over time and continues to improve. They added that people with multiple myeloma have heterogenous outcomes, with some people living for 10 to 15 years in complete remission after an autologous stem

cell transplant. They added that there was likely to be some overlap between the population in Giri et al. and the population that would be considered eligible for elranatamab. The committee noted that Giri et al. was an older study that included data collected between 1989 and 2014. It considered that the population in Giri et al. was likely to have a lower risk of death than the population eligible for elranatamab after 3 lines of treatment. Although the committee had significant reservations about the applicability of SMRs derived from Giri et al., it noted that the EAG's scenario was not supported by evidence. The committee further noted that when its preferred base-case assumptions for PFS and OS were used, the SMR adjustment no longer applied to the PFS curve. It noted that the SMR adjustment still impacted the OS curve but less so than in the company's base case. The committee concluded that it could accept the company's SMRs based on Giri et al. without this having a large impact on the cost-effectiveness results. It added that the company's SMRs were likely to be an underestimate, and this remained an area of uncertainty.

Time to treatment discontinuation for POM+DEX

3.9 The company modelled TTD for elranatamab by fitting parametric curves directly to the TTD data from the MagnetisMM-3 trial. For POM+DEX, the company's preferred approach was to calculate a multiplier based on the ratio between median TTD and median PFS. This was because of a lack of suitable TTD data. The company's calculated multiplier of 1.18 was applied as a hazard ratio to the POM+DEX PFS curve. The EAG highlighted that the company had used incorrect data to calculate the multiplier, noting that the company had used median time-to-progression data rather than median TTD. The EAG recalculated the multiplier using the correct inputs, which resulted in a multiplier of 0.725. The EAG noted that a multiplier of 0.725 was also applied in NICE's technology appraisal guidance on pomalidomide for multiple myeloma previously treated with lenalidomide and bortezomib (TA427). The committee agreed with the EAG that this was a factual error in the company's model. It agreed that

empirical data should be used, and that the multiplier should be calculated in line with the committee's preferred assumptions in TA427. The committee concluded that a hazard ratio of 0.725 should be applied to the POM+DEX PFS curve to determine TTD for POM+DEX.

Comparison of elranatamab with PANO+BORT+DEX

3.10 In its response to consultation, the company provided an unanchored MAIC comparing elranatamab with PANO+BORT+DEX based on data from PANORAMA-2. This was a phase 2, single-arm study of PANO+BORT+DEX in relapsed and bortezomib-refractory multiple myeloma. The results of the company's MAIC indicated that elranatamab reduced the risk of disease progression. (The company marked the results as confidential, so they cannot be presented here.) The company considered that the results of the MAIC overestimated OS for PANO+BORT+DEX. So, they applied a further adjustment to align the extrapolation with real-world evidence. The EAG acknowledged that there is no ideal method for comparison. This is because the populations included in the trials were very different in terms of when the trials were done and the treatments people had previously had. But it agreed with the company that the modelled OS for PANO+BORT+DEX was implausibly high when the outputs from the MAIC were used without adjustment, especially given the results for PFS. During the second committee meeting, the clinical expert also commented that the adjusted MAIC was more realistic. The committee considered that the company's methods for the OS comparison were questionable. It noted that the company had done a MAIC but had then crudely adjusted the PANO+BORT+DEX data to reduce survival to align with real-world evidence. This crude adjustment nullified the MAIC, resulting in a naive comparison of elranatamab and PANO+BORT+DEX. The committee noted that such a comparison may be biased in favour of elranatamab. This is because survival data with elranatamab still came from the clinical trial, and clinical trial populations are generally fitter. The committee agreed that the MAIC was not credible and concluded that it could not accept it for the comparison of

elranatamab and PANO+BORT+DEX. But the committee had previously noted that in clinical practice only a small proportion of people would likely have PANO+BORT+DEX and this proportion was diminishing over time. So, the committee agreed to only focus on the comparators POM+DEX and SEL+DEX for this appraisal (see section 3.3).

Comparison of elranatamab with SEL+DEX

3.11 In its response to consultation, the company also provided an unanchored MAIC comparing elranatamab with SEL+DEX using data from the STORM trial. This was a phase 2b, single-arm, open-label, multicentre study. The results of the company's MAIC suggested that elranatamab significantly reduced the risk of progression and death. (The company marked the results as confidential and so they cannot be presented here.) The company then applied the treatment effect from the MAIC to the unadjusted MagnetisMM-3 cohort A curves. The EAG commented that the company's modelling approach for this comparison was convoluted and somewhat inconsistent. It added that a more intuitive approach would be to compare the treatments using the curves fitted to the STORM-weighted MagnetisMM-3 Kaplan–Meier data, and the curves fitted to the digitised STORM data. During the second committee meeting, the company acknowledged the limitations of its modelling approach and agreed with the EAG's suggested alternative approach. The committee acknowledged the limited time the committee and the EAG had to incorporate and review this additional comparison. It concluded that the results of the unanchored MAIC with SEL+DEX were informative but uncertain.

Costs

Intravenous immunoglobulin use with elranatamab

3.12 People in the MagnetisMM-3 trial could have intravenous immunoglobulin (IVIg) to prevent or treat infections. In total, during trial follow up, 53 (43.1%) people had IVIg. In its original submission, the company assumed a lower number of people would have IVIg in clinical practice.

(The company considers the exact number to be confidential, so it cannot be reported here.) The company said that this was because of the NHS clinical commissioning policy for IVIg use that was in place at the time of the company submission. The policy did not permit preventative IVIg use for people having bispecific antibodies for multiple myeloma outside of clinical trials. The EAG noted that assuming no preventative IVIg use would mean that people having elranatamab in clinical practice would likely have a higher infection rate than people in the MagnetisMM-3 trial and the company's model. The clinical experts at the first committee meeting noted that the summary of product characteristics (SmPC) for elranatamab states that immunoglobulin levels should be monitored during treatment, and IVIg considered if immunoglobulin G (IgG) levels fall below 4 g/litre. Experts added that in clinical practice IVIg use and duration are likely to be above the company's estimates and that they would seek approval for IVIg use if this was considered necessary to prevent infection. The NHS England Cancer Drugs Fund clinical lead explained that NHS England would likely be open to preventative use of IVIg for people having elranatamab because this is included in elranatamab's marketing authorisation. So, the company's assumption that preventative IVIg would not be available on the NHS may have been incorrect. The committee noted that the high rates of grade 3 to 4 infection in MagnetisMM-3 meant that preventing infection with IVIg would be important. The committee noted that the company's modelling approach was inconsistent. The company had modelled a lower number of people having IVIg compared with the trial and lower IVIg costs. But the company had not modelled the increased infection rate and cost and utility impact of infection that would likely result from reduced IVIg use. The committee considered that ideally the number of people having IVIg should reflect the MagnetisMM-3 study. The committee further considered that because of the short follow up in MagnetisMM-3, IVIg use and duration could have been underestimated. It added that it was likely that the infection risk would persist and potentially increase over time, and so with more follow-

up data, the number of people having IVIg and the duration of IVIg treatment could increase. So, the committee concluded that the company may have underestimated IVIg use, and this remained an area of uncertainty.

Relative dose intensity for elranatamab

3.13 Drug acquisition and administration costs in the company's model were multiplied by a relative dose intensity (RDI) to account for dose reductions and interruptions. The RDI was calculated for elranatamab based on observed data in the MagnetisMM-3 trial. (The company considers the exact figure to be confidential, so it cannot be reported here.) The EAG was uncertain whether the RDI seen over the follow-up period in MagnetisMM-3 would apply over the remaining time horizon. The EAG was also unclear how dose reductions would translate into drug and administration cost savings. This is because vial sizes are fixed and administration costs are a discrete unit of resource, which would not be expected to decrease if the dose was reduced. The company explained in response to the factual accuracy check that RDI in MagnetisMM-3 was driven more by dose interruptions than dose reductions. The clinical experts at the first committee meeting explained that people having existing multiple myeloma treatments may interrupt doses because of toxicity or for personal reasons, but doses are not generally reduced. They further noted that the SmPC for elranatamab states that dose reductions are not recommended, but dose delays may be needed to manage toxicities and infections. The committee considered that elranatamab dosing in clinical practice would align with the SmPC, and doses would be interrupted rather than reduced. It further noted that interruptions would continue while people remained on treatment and at risk of adverse events. The committee concluded that the company's RDI based on data from MagnetisMM-3 was appropriate and that this should apply for the duration of elranatamab treatment.

Stopping rule for elranatamab

3.14 The company applied a stopping rule for elranatamab at 3 years. It claimed that the greater-than-expected discrepancy between the PFS and TTD curves showed that when people stop treatment, the benefits are maintained. It added that applying a stopping rule balanced long-term risks of remaining on treatment with ongoing efficacy. The EAG was concerned about the validity of the stopping rule given the lack of long-term data. It was also uncertain what impact stopping treatment may have on efficacy. At the first committee meeting, 1 patient expert said that a stopping rule would likely be challenged by people if they are still benefiting from the treatment at 3 years. One clinical expert explained that it was difficult to know how stopping treatment would affect outcomes without any data on this. But they said that there may be a theoretical benefit of having a fixed treatment duration to prevent T-cell exhaustion, a recognised cause of treatment failure. The committee noted that the SmPC for elranatamab states that treatment should be continued until disease progression or unacceptable toxicity. It noted that the company's stopping rule was not supported by evidence or stated in the SmPC. The committee considered that if T-cell exhaustion were to occur, then the benefit of elranatamab would also be reduced as well as the cost, which the company did not model. The committee considered that recommending elranatamab without a stopping rule would not prevent clinicians, and people having elranatamab, from stopping treatment if they thought it was appropriate to do so. So, the committee concluded that the company's stopping rule should not apply.

Subsequent treatments – comparison with SEL+DEX

3.15 The EAG highlighted that the company had not updated the subsequent treatment assumptions in its comparison with SEL+DEX, and that the inputs for the POM+DEX comparison remained. The EAG preferred to reduce the proportion who move onto any subsequent treatment to 20%, and changed the distribution so that only cyclophosphamide was

considered a relevant subsequent treatment. This aligned with the assumptions used in TA970. It also updated the subsequent treatment duration to 4.8 months to align with the POM+DEX arm. The company and the committee were satisfied with the EAG's updated approach for the comparison with SEL+DEX. Although, the committee recognised that the assumption of updating the subsequent treatment duration to 4.8 months to align with the POM+DEX arm was arbitrary.

Other issues with minor impacts on cost-effectiveness results

3.16 In addition to the key issues discussed in sections 3.7 to 3.15, the EAG also made several minor changes to the company's base-case modelling approaches and assumptions (see the EAG report in the committee papers). The additional changes were considered, and it was agreed that the EAG's approaches were reasonable. These were:

- For end-of-life costs, the EAG's approach was preferred because it was more closely aligned with the preferred approach in TA427.
- The company's approach of assuming only 1 week of end-of-life care was considered an underestimate.
- For the method of applying IVIg costs in the model, the EAG's simplified approach was preferred, to avoid double counting.
- For the RDI for POM+DEX, the EAG approach was preferred, to align with the committee's agreed assumptions for POM+DEX in TA427.

The committee concluded that the EAG's additional changes to the company base case were appropriate and that these only had a minor impact on cost-effectiveness results.

Severity

3.17 The committee considered the severity of the condition (the future health lost by people living with the condition and having standard care in the NHS). The committee may apply a greater weight to QALYs (a severity modifier) if technologies are indicated for conditions with a high degree of

severity. The company calculated absolute and proportional QALY shortfall estimates using the QALY shortfall calculator published by Schneider et al. (2021). Based on this calculation, a severity modifier of 1.2 was applied for all comparisons. The EAG agreed with the company's calculation of the severity modifier. The committee noted that in the appraisal for SEL+DEX (TA970) a severity modifier of 1.7 was used. But the committee concluded that a severity modifier of 1.2 was appropriate based on the QALY shortfall calculation for this appraisal.

Cost-effectiveness estimates

Acceptable ICER

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

- lack of long-term PFS and OS data for elranatamab (see section 3.4)
- lack of long-term data on IVIg use and IVIg treatment duration (see section 3.12)
- lack of a direct comparison between elranatamab and the comparators (see sections 3.5, 3.10 and 3.11).

Because of confidential discounts for elranatamab and the comparators, all cost-effectiveness results are commercial in confidence and cannot be reported here. The committee considered that, because the evidence base was immature and there was no randomised-controlled trial data, the most plausible ICERs were

uncertain. The committee also noted that there were benefits of elranatamab that had not been captured in the economic modelling. It noted that elranatamab was an innovative treatment with a novel mechanism of action. It considered that the steroid-sparing nature of the treatment was a distinct advantage. So, the committee concluded that an acceptable ICER would be around the middle of the range NICE considers a cost-effective use of NHS resources (£20,000 to £30,000 per QALY gained).

Committee's preferred assumptions

3.19 The committee's preferred assumptions included:

- a gamma distribution for modelling PFS for elranatamab in the comparison with POM+DEX (see section 3.7)
- a generalised gamma distribution for modelling OS for elranatamab in the comparison with POM+DEX (see section 3.7)
- time-varying SMRs based on Giri et al. (2021), conditional on the gamma and generalised gamma distributions being selected for PFS and OS in the comparison with POM+DEX (see section 3.8)
- the ratio between TTD and PFS for POM+DEX to be 0.725 (see section 3.9)
- the number of people having IVIg to be between the company's estimate and 43.1% (see section 3.12)
- the RDI for elranatamab to be the company's estimate for the duration of treatment (see section 3.13)
- having no stopping rule (see section 3.14)
- using the EAG's approach to modelling subsequent treatments for SEL+DEX (see section 3.15)
- several other assumptions with a minor impact on the ICER (see section 3.16).

The committee considered a range of ICERs for elranatamab. With its preferred assumptions and a 1.2 severity weighting, the cost-

effectiveness results compared with POM+DEX and SEL+DEX were above the range that NICE considers an acceptable use of NHS resources. Because of this, the committee could not make a recommendation for routine commissioning.

Managed access

Recommendation with managed access

3.20 Having concluded that elranatamab could not be recommended for routine use, the committee considered if it could be recommended with managed access for treating refractory multiple myeloma after 3 or more lines of treatment. It discussed that:

- The key uncertainties that could be resolved with managed access were the:
  - immaturity of the data from the clinical trial
  - lack of long-term data on the number of people having IVIg
  - lack of long-term data on the duration of IVIg treatment.
- The committee noted that the MagnetisMM-3 study was still ongoing.
- The committee considered that further data collection with managed access could address some of the clinical uncertainty:
  - MagnetisMM-3 is due to finish in December 2025. Longer-term follow-up data could help reduce uncertainties in estimating long-term PFS and OS and provide further data on the RDI of elranatamab.
  - The Systemic Anti-Cancer Therapy dataset could be used to collect evidence on clinical outcomes for people having elranatamab in the NHS.
  - The MDSAS (medical data solutions and services) immunoglobulin database could be used to collect evidence on use and duration of IVIg.
  - Other studies that may provide helpful additional data include MM-15 and MM-16.

- The company submitted a managed access proposal and expressed an interest in elranatamab being considered for managed access. The managed access feasibility assessment noted that elranatamab would likely be eligible for use in the Cancer Drugs Fund.
- Using the committee's preferred assumptions elranatamab has plausible potential to be cost effective.

The committee concluded that elranatamab met the criteria to be considered for a recommendation with managed access. It recommended elranatamab for use with managed access as an option for treating relapsed and refractory multiple myeloma in adults after 3 or more lines of treatment if the conditions in the managed access agreement are followed. When the guidance is reviewed, the company should use the committee's preferred assumptions (unless new evidence indicates otherwise).

Other factors

Equality

3.21 The committee did not identify any equality issues. In its submission, the company stated that making a recommendation by line of treatment would create inequalities in treatment access for people whose multiple myeloma becomes triple-class refractory at third line or earlier. The committee did not consider this an equality issue because it does not relate to any of the protected characteristics under the Equality Act 2010.

4 Implementation

4.1 When NICE recommends a treatment as an option for use with managed access, 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 healthcare professional responsible for their care thinks that elranatamab is the right treatment, it

should be available for use, in line with NICE's recommendations and the criteria in the managed access agreement.

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 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 with managed access. When a NICE technology appraisal guidance recommends the use of a drug or treatment, or other technology, for use with managed access, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final draft guidance or agreement of a managed access agreement by the NHS in Wales, whichever is the later.

5 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 and a project manager.

Madiha Adam and Anna Willis
Technical leads

Joanna Richardson
Technical adviser

Vonda Murray
Project manager

ISBN: [to be added at publication]