NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

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

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using elranatamab 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: July 2024

Note that this document is not NICE's final guidance on elranatamab. 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- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using elranatamab in the NHS in England.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: 9 August 2024
- Second evaluation committee meeting: Date to be confirmed
- Details of the evaluation committee are given in section 4.

1 Recommendations

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

- pomalidomide plus dexamethasone would otherwise be offered, and
- 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 treatment most commonly used for relapsed and refractory multiple myeloma after 3 lines of treatment (including an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 antibody) is pomalidomide plus dexamethasone. For this evaluation, the company asked for elranatamab to only be considered as an alternative to pomalidomide plus dexamethasone. This does not include everyone who it is licensed for.

Evidence from a clinical trial for elranatamab is promising, but it was not compared with other treatments and the trial is still ongoing. So, the effectiveness of elranatamab and its long-term benefits are uncertain. The results from this trial were used for an indirect comparison with pomalidomide plus dexamethasone. It suggests that elranatamab could increase how long people have before their condition gets worse and how long they live compared with pomalidomide plus dexamethasone.

But the results are uncertain because it was based on the uncertain elranatamab trial data.

Because of the uncertainty in the long-term benefits of elranatamab, and in the long-term use of intravenous immunoglobulin in people having elranatamab, the cost-effectiveness estimates are also highly uncertain. So, it cannot be recommended for routine use in the NHS.

Elranatamab could be cost effective if further evidence shows that people live longer with treatment. Longer-term evidence from the trial and NHS practice could help address the remaining uncertainties. So, elranatamab is recommended for use with managed access if it is used only as an alternative to pomalidomide plus dexamethasone.

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; dictionary of medicines and devices, accessed May 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 stated 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 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 with 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 to people with the condition. Patient experts reported that elranatamab does not have to be used in combination with steroids, unlike 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 weekly, every 2 weeks, then eventually once a month. The patient experts explained how avoiding lengthy and frequent hospital visits would be welcomed by people with multiple myeloma, their families and hospital staff. This is a distinct advantage of elranatamab compared to some other multiple myeloma treatments. 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 a proteasome inhibitor, an immunomodulatory drug and an anti-CD38 monoclonal antibody. The condition must have also progressed on the last treatment. The company stated that most people eligible for elranatamab according to the marketing authorisation would have had 3 or more previous lines of treatment. But around 10% of people could be considered eligible for elranatamab after 2 previous lines of treatment. This is because the multiple myeloma treatment pathway has evolved over time and there are now combination treatments available at earlier stages in the pathway. But the company submission only provided a comparison with

pomalidomide plus dexamethasone (POM + DEX), which is currently used as a fourth line treatment. This was deemed the most appropriate comparator by the company's clinical experts and was supported by real-world evidence. The company further explained that people may be eligible for elranatamab according to the marketing authorisation if they have had 3 previous treatments (triple-class exposed) while only being refractory to the last treatment. The company acknowledged that the population of the MagnetisMM-3 trial was narrower than the marketing authorisation because it only included people whose condition was refractory to all 3 treatments (that is, triple-class refractory). One of the clinical experts explained the difficulties in determining which classes of drugs multiple myeloma is refractory to, as many drugs are given in combination with drugs from a different class at earlier lines. But the clinical experts agreed that most people having fourth line treatment had myeloma that was triple-class refractory. The committee agreed with the clinical experts that it would be difficult to determine which classes of drugs people were refractory to in clinical practice. So, it concluded that it would not be appropriate to restrict treatment to people with multiple myeloma that is triple-class refractory. The committee then considered whether elranatamab should be recommended in line with the full marketing authorisation. The NHS England Cancer Drugs Fund (CDF) clinical lead explained that, as the company had only presented a comparison with POM + DEX, elranatamab could only be considered at fourth line or later. The committee agreed that company's comparison with POM + DEX alone, and not with any treatments used at third line, meant that the effectiveness (and cost-effectiveness) of elranatamab in the third line setting was unknown. Clinical experts attending the committee meeting were not concerned about elranatamab only being recommended as a fourth line treatment, as people eligible earlier in the pathway would still be able to access elranatamab by using other treatments to bridge the gap between third line and fourth line. The committee concluded that it would evaluate elranatamab after at least 3 lines of treatment in people

whose condition was refractory to the last line of treatment. Previous treatments should have included a proteasome inhibitor, an immunomodulatory drug and an anti-CD38 monoclonal antibody. It added that elranatamab should be used only if POM + DEX would otherwise have been considered.

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 proteasome inhibitor, 1 immunomodulatory drug, 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 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. The company explained that additional data from a later data cut is now available and supports the 15-month data but this had not been shown to committee. The company explained that the estimated completion date for MagnetisMM-3 has been extended to December 2025. The committee considered that very little data was currently available for elranatamab, because of the short follow up in the data cut presented in the company submission. The committee was aware of recently published real-world evidence for elranatamab, Costa et al. 2024, but it noted that the company had not provided data from this study in its submission. The committee noted that because of elranatamab's novel mechanism of action, it had received its marketing authorisation sooner than usual, so was being

evaluated very early. The committee concluded that the results from MagnetisMM-3 appeared promising, but the data is immature. This means that there is substantial uncertainty around the 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 was triple-class refractory. As discussed in section 3.3, clinical experts expected that many people treated at fourth line in clinical practice would be triple-class refractory, but some may be triple-class exposed and refractory to the last treatment only. The committee concluded that results of MagnetisMM-3 may not be generalisable to people who were triple-class exposed but not triple-class refractory, but it noted that this was likely to be a small number of people.

Comparison of elranatamab with POM + DEX

3.5 The clinical evidence for POM + DEX came from MM-003. This was a phase 3, randomised, open-label study in people with relapsed, refractory multiple myeloma who had received at least 2 lines of lenalidomide and bortezomib alone or in combination. 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 highly uncertain.

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 (section 3.7 to section 3.9). 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.

Progression-free and overall survival extrapolations for elranatamab

3.7 To estimate long-term PFS and OS, 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 OS and PFS. The company's OS and PFS 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 dead 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 OS and PFS curves did not converge, maintaining a proportion of people in the post-progression health state over time. The EAG also provided a scenario which used the unanchored MAIC hazard ratios applied to the POM + DEX curves to estimate OS and PFS for elranatamab. Clinical experts attending 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 expressed that 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 15-month follow-up data provided. 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 OS and PFS 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 which 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 OS and PFS 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 OS and PFS were highly uncertain given the immaturity of the data, but the EAG's base-case extrapolations were the most plausible of the options presented.

Standardised mortality ratio adjustment

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. is 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 which 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 with 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 is considered that the population in Giri et al. were likely to be a better risk group 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 OS and PFS were used (section 3.7), 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 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 the NICE 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.

Costs

Intravenous immunoglobulin use

3.10 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 submission, the company assumed a lower number of people would have IVIG in clinical practice (the exact number is considered confidential by the company and cannot be reported here). The company stated that this was because of the NHS clinical commissioning policy for IVIG use 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 company's model. Clinical experts at the 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 400 mg/dl. 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 CDF 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 be 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

3.11 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 exact figure is considered confidential by the company and 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 proportions with dose interruptions and dose reductions are considered confidential by the company and cannot be reported here. Clinical experts at the 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

3.12 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 shows that when people stop treatment, the benefits are

maintained. It added that applying a stopping rule balances 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. One patient expert stated 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 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.

Other issues with minor impacts on the ICER

3.13 In addition to the key issues discussed in section 3.7 to section 3.12, 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. For end-of-life costs, the EAG's approach was preferred because it was more 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

3.14 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 the median age of the population in MagnetisMM-3 of 67.1 years, expected QALYs for a healthy individual in the general population were 10.22. Total QALYs for people having standard treatment with POM + DEX were 0.89. This meant that the absolute shortfall was 9.33 and the proportional shortfall was 0.90. So, the company's resulting proportional shortfall was within the 0.85 to 0.95 threshold range specified in section 6.2 of NICE's health technology evaluations manual for a severity weighting of 1.2. The EAG agreed with the company's calculation of the severity modifier. The committee concluded that a severity modifier of 1.2 was appropriate.

Cost-effectiveness estimates

Committee preferred assumptions

3.15 NICE's manual on health technology evaluations notes that, above a most plausible 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 OS and PFS data for elranatamab (section 3.7)
- lack of long-term data on IVIG use and IVIG treatment duration (section 3.10)
- lack of a direct comparison between elranatamab and POM + DEX (section 3.5)

Because of confidential discounts for elranatamab and POM + DEX, all cost-effectiveness results are commercial in confidence and cannot be reported here. The committee's preferred assumptions included:

- gamma distribution for modelling PFS for elranatamab (section 3.7)
- generalised gamma distribution for modelling OS for elranatamab (section 3.7)
- time-varying SMRs based on Giri et al., conditional on the gamma and generalised gamma distributions being selected for PFS and OS (section 3.8)
- ratio between TTD and PFS for POM + DEX: 0.725 (section 3.9)
- number of people having IVIG: between the company's estimate and 43.1% (section 3.10)
- RDI for elranatamab: company's estimate for the duration of treatment (section 3.11)
- no stopping rule (section 3.12)
- several other assumptions with a minor impact on the incremental cost-effectiveness ratio (ICER) (section 3.13).

The committee considered that the evidence base was immature and the lack of data from a randomised controlled trial meant that the most plausible ICER was highly uncertain. Because of the high uncertainty, the committee could not make a recommendation for routine commissioning.

Managed access

Recommendation with managed access

3.16 Having concluded that elranatamab could not be recommended for routine use, the committee considered if it could be recommended with managed access. Elranatamab would be used for treating relapsed and refractory multiple myeloma in adults after 3 or more lines of treatment (including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody), and when POM + DEX would otherwise be offered. It discussed that:

- The key uncertainties that could be resolved with managed access relate to the immaturity of the data from the clinical trial, the lack of long-term data on the number of people having IVIG, and the duration of IVIG treatment.
- The committee noted that the MagnetisMM-3 study was still ongoing. At the March 2023 data cut, median OS and PFS had not been reached.
- 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 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 immunoglobulin database (MDSAS) could be used to collect evidence on use and duration of IVIG.
  - Other studies which 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 CDF.

- 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), as set out in section 3.15.

Other factors

Equality

3.17 The committee did not identify any equality issues. The company stated that making a recommendation by line of treatment would create inequalities in treatment access for people who become triple-class refractory at third line or earlier. The committee did not consider this an equality issue because it did 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.

Anna Willis

Technical lead

Joanna Richardson

Technical adviser

Vonda Murray

Project manager

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