NICE National Institute for Health and Care Excellence

NICE guidance

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

Technology appraisal guidance
Published: 3 December 2025

www.nice.org.uk/guidance/ta1114

Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

1 Recommendations

1.1 Talquetamab can be used as an option to treat relapsed and refractory multiple myeloma in adults when:

- they have had 3 or more lines of treatment including:
  - an immunomodulatory drug
  - a proteasome inhibitor, and
  - an anti-CD38 antibody, and
- the myeloma has progressed on the last treatment.

Talquetamab can only be used if the company provides it according to the commercial arrangement.

1.2 This recommendation is not intended to affect treatment with talquetamab 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

Talquetamab must be funded in the NHS in England for the condition and population in the recommendations, if it is considered the most suitable treatment option. Talquetamab must be funded in England within 90 days of final publication of this guidance.

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

NICE has produced tools and resources to support the implementation of this guidance.

Why the committee made these recommendations

For this evaluation, the company compared talquetamab with teclistamab. Teclistamab is one of the standard treatments for multiple myeloma that has relapsed (come back) and is refractory (has stopped responding to treatment) after 3 or more lines of treatment and that has progressed on the last treatment. Using teclistamab or talquetamab only after 3 lines of treatment is narrower than the marketing authorisations, which specify use after 3 treatments.

The evidence from clinical trials is uncertain because:

- the teclistamab trial was done during the COVID-19 pandemic, which could have affected the number of deaths
- some people in the trials had treatments after teclistamab or talquetamab that are not available in the NHS.

But the results from an indirect comparison suggest that talquetamab increases how long people live compared with teclistamab, and real-world evidence supports this.

The most likely cost-effectiveness estimates are within the range that NICE considers an acceptable use of NHS resources. So, talquetamab can be used.

2 Information about talquetamab

Marketing authorisation indication

2.1 Talquetamab (Talvey, Johnson & Johnson Innovative Medicine) is indicated 'as monotherapy for the treatment of adult patients with relapsed and refractory multiple myeloma, who have received at least 3 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 talquetamab.

Price

2.3 The list price for talquetamab is £326.41 per 3-mg vial and £4,352.00 per 40-mg vial (excluding VAT, BNF online accessed October 2025).

2.4 The company has a commercial arrangement. This makes talquetamab available to the NHS with a discount. The size of the discount is commercial in confidence.

Carbon Reduction Plan

2.5 For information, the Carbon Reduction Plan for UK carbon emissions is published on Johnson & Johnson Innovative Medicine's webpage on their responsibility to the planet.

3 Committee discussion

The evaluation committee considered evidence submitted by Johnson & Johnson Innovative Medicine, 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 the 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, because people are aware that treatment options and life expectancy reduce with each relapse. The patient expert at the first committee meeting explained the negative impact of frequent relapses of multiple myeloma. They spoke about the anxiety around the availability of treatment options after each relapse. They also spoke about the anxiety around having to take corticosteroids, which are associated with a considerable negative impact on quality of life. The committee recognised the substantial impact that multiple myeloma has on survival and quality of life. It acknowledged the unmet need for more treatments that are effective for people who have already had several treatments.

Clinical management

Treatment pathway, positioning and comparators

3.2 According to the marketing authorisation, people having talquetamab 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 submission provided a

comparison with teclistamab, a treatment at fourth line and beyond. Clinical advice to the EAG was that teclistamab is the most relevant comparator for this evaluation, given the company's positioning after 3 or more lines of treatment. The clinical experts at the first committee meeting agreed that teclistamab is the most frequently used fourth-line treatment option for relapsed and refractory multiple myeloma and a relevant comparator to talquetamab. But the NHS England Cancer Drugs Fund clinical lead explained that most people have pomalidomide plus dexamethasone and daratumumab at fourth line, with teclistamab mostly being used at fifth line. They also noted that the treatment pathway was rapidly evolving and that the data informing treatment use may change as newer treatments are implemented into the pathway. The committee noted that teclistamab is an available option after 3 or more lines of treatment (see NICE's technology appraisal guidance on teclistamab for treating relapsed and refractory multiple myeloma after 3 or more treatments [TA1015]). It also noted that elranatamab is available for treating relapsed and refractory multiple myeloma after 3 or more lines of treatment. But elranatamab is only recommended for use within the Cancer Drugs Fund (see NICE's technology appraisal guidance on elranatamab for treating relapsed and refractory multiple myeloma after 3 or more treatments). So, it cannot be considered a comparator to talquetamab in this appraisal. The committee concluded that teclistamab is the most relevant comparator to talquetamab for this evaluation.

Clinical effectiveness

Talquetamab clinical trial data

3.3 The key clinical-effectiveness evidence for talquetamab came from the MonumenTAL-1 trial. This is an ongoing phase 1 and 2, single-arm, open-label, multicentre study. People in the trial have triple-class-exposed relapsed and refractory multiple myeloma that is refractory to at least 1 proteasome inhibitor, 1 immunomodulatory drug and 1 anti-CD38 monoclonal antibody. The company presented data for cohort C only (n=154). The company stated, based on its clinical advice, that most (90%) of people in UK clinical practice will have talquetamab once every 2 weeks (cohort C) with 10% having it once weekly (cohort A; n=143). It presented data from the September 2024 data cut, with a

median follow up of 31.2 months. The overall response rate was 69.5%. Median overall survival was not estimable and median progression-free survival was 11.2 months. The committee noted that the marketing authorisation allows talquetamab to be used once weekly or once every 2 weeks. So, it questioned whether the clinical-effectiveness evidence from cohort A was appropriately captured in the company's submission. It also noted that there was a difference in clinical effectiveness with a reduced median progression-free survival for cohort A (7.5 months) than for cohort C. The company said that the once every 2 weeks dosage in cohort C is more convenient for people and would likely increase the cost effectiveness of talquetamab. A clinical expert said that about 90% of people have the once every 2 weeks dosage in NHS clinical practice because of its convenience over the once weekly dosing regimen. So, it may be appropriate to model resource use according to 90% of dosing regimens being once every 2 weeks and 10% being once weekly. But the committee was unclear why the clinical efficacy would differ markedly between these 2 dosing regimens. So, the committee said that it would also like to see clinical and cost-effectiveness analyses on pooled data.

In response to consultation, the company provided pooled data for cohorts A and C. This meant that the committee now had clinical-effectiveness results for:

- cohort C alone
- all pooled cohort-A and cohort-C data
- a weighted sample of the pooled data, of 90% cohort C and 10% cohort A.

The committee noted that the company had only provided cost-effectiveness results for cohort C alone and for the pooled data using 90% cohort C and 10% cohort A. The company had not provided cost-effectiveness results for all pooled cohort-A and cohort-C data. The committee considered which was the most appropriate cohort for decision making. It noted the reduced clinical effectiveness in cohort A and that using cohort C alone reduced the sample size in the evidence base. The committee questioned the reasons for the lower clinical effectiveness in cohort A compared with cohort C. The clinical experts at the second committee meeting explained that there were more dose delays and modifications in cohort A. They also said that the once every 2 weeks dosing in cohort C causes less T-cell exhaustion and allows for more

T-cell recovery. They explained the patient preference for once every 2 weeks dosing in clinical practice and said that this is also likely to have reduced healthcare-resource impact. The company also explained that they did not provide cost-effectiveness results using all pooled cohort-A and cohort-C data because only cohort C is relevant to clinical practice. It said that this dosing provides the best clinical outcomes for people with multiple myeloma. The committee agreed that most people would have the treatment once every 2 weeks in clinical practice, but it decided that the more frequent dosing in cohort A was relevant for informing the overall treatment effect. This was because there is uncertainty that the mechanistic explanations for T-cell recovery in the intervals would result in the benefits seen in cohort C. So, the committee concluded that all the available evidence should be pooled.

Teclistamab clinical trial data

3.4 The clinical-effectiveness evidence for teclistamab came from MajesTEC-1, an ongoing phase 1 and 2, single-arm, open-label, multicentre trial. People in the trial have triple-class-exposed relapsed or refractory multiple myeloma that is refractory to at least 1 proteasome inhibitor, 1 immunomodulatory drug and 1 anti-CD38 monoclonal antibody. The company presented data from the phase 1 part 2 cohort and the phase 2 cohort A of the study (n=165). It presented data from the August 2023 data cut, with a median follow up of 30.4 months. The overall response rate was 63%. Median overall survival was 22.2 months and median progression-free survival was 11.4 months.

Comparing talquetamab with teclistamab

Indirect treatment comparison methods and results

3.5 In the absence of direct clinical trial evidence comparing talquetamab with teclistamab, the company did an indirect treatment comparison. It did this to estimate the comparative effectiveness for the relevant patient population using data from MonumenTAL-1 and MajesTEC-1. The company identified 17 covariates,

of which 5 were considered priority prognostic factors and were adjusted for using inverse probability of treatment weighting (IPTW). The company used the average treatment effect for the treated (ATT) method to re-weight the baseline characteristics of the MajesTEC-1 cohort to match those of MonumenTAL-1. The results of the indirect treatment comparison for progression-free survival showed that talquetamab had a non-significant improvement compared with teclistamab. The hazard ratio for progression-free survival is considered confidential by the company and cannot be reported here. For the overall-survival analyses from the indirect treatment comparison, MonumenTAL-1 and MajesTEC-1 data was adjusted using a 2-stage adjustment. This was done to remove the effects of the subsequent treatments not routinely available in UK clinical practice (see section 3.13). The results of the indirect treatment comparison showed a significant improvement in overall survival for talquetamab compared with teclistamab. The hazard ratio for overall survival is considered confidential by the company and cannot be reported here.

In response to consultation the company provided an updated indirect treatment comparison using, from MonumenTAL-1:

- the pooled, unadjusted cohort-A and cohort-C data
- the weighted sample of the pooled data using 90% cohort C and 10% cohort A.

  The company noted that the indirect treatment comparison results using pooled data were consistent with its base case, which used cohort C alone. The EAG explained that the company's indirect treatment comparison results, particularly the overall-survival hazard ratio, were very uncertain and noted several limitations (see sections 3.6 to 3.8). In the absence of access to patient-level overall-survival data from the clinical trials, the EAG could not run its own analyses. So, it used the overall-survival hazard ratio from the indirect treatment comparison in its base case. But the EAG explained that the clinical effectiveness of talquetamab compared with teclistamab, particularly the overall-survival hazard ratio, was highly uncertain and should be interpreted with caution. It provided scenario analyses that varied the overall-survival hazard ratio to demonstrate the impact on the cost-effectiveness results.

Uncertainties in the indirect treatment comparison

Early separation of the overall-survival curves

3.6 At the first committee meeting, the committee noted that the company's indirect treatment comparison results demonstrate a significantly large benefit in overall survival with talquetamab compared with teclistamab. The EAG noted that there is notable separation from the start of the overall-survival Kaplan–Meier curves for talquetamab and teclistamab from the indirect treatment comparison. This is not the case for the progression-free survival Kaplan–Meier curves for talquetamab and teclistamab, which are similar to each other and close together. The company said that the overall-survival benefit for talquetamab is driven by the difference in antibody target, with significantly fewer infections associated with talquetamab compared with teclistamab. The company also said that there were fewer adverse-event related deaths in MonumenTAL-1 compared with MajesTEC-1. The clinical experts at the first committee meeting agreed that the overall-survival benefit is likely associated with having considerably fewer infections with talquetamab compared with teclistamab. They said that this is reflected in the higher overall-survival benefit seen in MonumenTAL-1 compared with in MajesTEC-1. But the clinical experts acknowledged that a large overall-survival benefit early in the clinical data is unusual and they would normally expect to see this later.

At the second committee meeting, the company explained that in the first 3 months there were more than twice as many deaths in MajesTEC-1 from disease progression compared with MonumenTAL-1. The company said that this is supported by the faster response with talquetamab because of its novel target which is different to that of teclistamab. The EAG advised that the company response does not fully explain the early separation in overall-survival curves for teclistamab and talquetamab, compared to progression-free survival. The committee considered the advice from the clinical experts on infection risk for people having teclistamab. The committee decided it was plausible for the progression-free survival to be similar for the 2 technologies, yet for there to be reduced overall survival for teclistamab. But it concluded that this did not explain the magnitude of the early separation of the overall-survival curves.

Lack of correlation between progression-free survival and overall survival

3.7 At the first committee meeting, the EAG noted that regression-analysis studies on overall survival and progression-free survival (Etekal et al. 2023 and Cartier et al. 2015) indicate that the company's overall-survival hazard ratio is an outlier and is more favourable to talquetamab than would be expected given the progression-free survival hazard ratio. The EAG said that this suggests a lack of correlation between overall survival and progression-free survival results from the company's indirect treatment comparison. The committee noted that the Etekal et al. regression analysis, which included treatments for relapsed or refractory multiple myeloma, identified a correlation of 0.76 (95% confidence interval [CI] 0.42 to 0.91) between progression-free and overall survival. This indicated a medium association between progression-free survival and overall survival. The committee recalled the non-significant progression-free survival hazard ratio of close to 1 from the company's indirect treatment comparison. It questioned how this translates to a large statistically significant overall-survival hazard ratio for talquetamab compared with teclistamab. The company said that people will be fitter after treatment with talquetamab compared with teclistamab, because B-cell maturation antigen (BCMA)-targeting treatments like teclistamab can cause T-cell exhaustion. So, people would be more likely to respond more effectively to subsequent treatments after talquetamab than after teclistamab. The clinical experts agreed that the overall-survival benefit is likely associated with people being fitter following disease progression on talquetamab in MonumenTAL-1 compared to teclistamab in MajesTEC-1. The clinical experts also explained the current difficulty in managing multiple myeloma that does not respond to treatment with teclistamab, which would be improved if people could go on to have talquetamab. The clinical experts further explained that the studies in the Etekal et al. regression analysis predate bispecific treatments such as teclistamab and talquetamab with their novel mechanism of action. So, they said that the Etekal et al. regression analysis may not be applicable. They noted that the overall-survival hazard ratio for teclistamab compared with pomalidomide plus dexamethasone from TA1015 is also an outlier. But the committee remained concerned because it is very rare to see a large overall-survival benefit with a treatment that has little demonstrated difference in progression-free survival. Instead, the committee expected overall survival may correlate with progression-free survival.

At the second committee meeting, the company provided additional analyses that

demonstrated that talquetamab shows improved outcomes for progression-free survival on a subsequent treatment. The EAG explained that the company's analysis of progression-free survival on a subsequent treatment is inequitable between the compared treatments. It explained that this is because the analysis does not censor for COVID-19-related deaths and relies on investigator assessment of progression rather than independent assessment. It also explained that adjustment for the impact of COVID-19 in the teclistamab arm, for both overall survival and progression-free survival, is uncertain and difficult to estimate. So, it said that understanding the pre-progression and post-progression survival (with different utility values attached in the cost-effectiveness analysis) remained problematic. The committee noted that most of the overall-survival benefit with talquetamab was accrued after progression. So, the committee questioned whether having subsequent teclistamab after initial talquetamab would affect the immunity benefit that talquetamab gives. A clinical expert at the second committee meeting explained that healthcare professionals like to add an immunomodulatory drug after 1 bispecific treatment to enable T-cell recovery before having an alternative bispecific. The clinical expert further explained that the condition is very difficult to treat when BCMA-targeting bispecific treatment has failed after a relapse. But they said that people whose condition progresses after talquetamab are generally fitter and can have subsequent treatment. The committee acknowledged that there may be some survival benefit with talquetamab after disease progression, but remained concerned about the size of this benefit.

Impact of COVID-19

3.8 The committee also noted the different timepoints at which the MajesTEC-1 and MonumenTAL-1 trials were done and the large difference in number of COVID-19-related deaths in the 2 trials. It questioned whether the timing of these trials in relation to COVID-19 accounted for the large overall-survival benefit seen with talquetamab. The EAG explained that the impact of COVID-19 on the overall survival of the unvaccinated MajesTEC-1 population (MajesTEC-1 was recruited to earlier in the pandemic, when the vaccine had not been fully rolled out) is not adjusted for and is likely to introduce some confounding in the company's indirect treatment comparison results. The clinical expert explained that there was likely a difference in the availability of COVID-19 vaccinations, accounting for the higher

number of all infections in MajesTEC-1 than in MonumenTAL-1. But they explained that of 94 deaths in MajesTEC-1, 72 or more were not related to COVID-19, and that most of these were related to disease progression. So, the clinical expert thought that COVID-19-related infections might not explain all of the overall-survival benefit seen with talquetamab. The committee noted that the company in TA1015 qualitatively considered that the overall-survival benefit for teclistamab in MajesTEC-1 may be underestimated. This was because the trial was done during the height of the pandemic before widespread COVID-19 vaccinations were available.

In response to consultation, the company updated the overall-survival hazard ratio in its base case by censoring the COVID-19-related deaths for people who had a complete response and no disease progression. The hazard ratio for overall survival is considered confidential by the company and cannot be reported here. The company also provided a scenario analysis in which all COVID-19-related deaths were censored. The company explained that both approaches resulted in an overall-survival hazard ratio that was consistent with the original, uncensored hazard ratio. It said that this was also consistent when using cohort C alone or the weighted cohort-A (10%) and cohort-C (90%) data. The EAG noted that the company's COVID-19 adjustments were an improvement but did not account for the full impact of COVID-19-related deaths. It explained that it would need data on the numbers of people fully vaccinated for COVID-19 for a reliable comparison between talquetamab and teclistamab, noting the large number of COVID-19-related deaths in the teclistamab arm. The EAG noted that censoring COVID-19 deaths had minimal impact on the overall-survival hazard ratio. It said that it would have expected the adjustment to have had a bigger effect had the impact of COVID-19 been appropriately adjusted for. The EAG considered that analyses comparing 'vaccinated' and 'unvaccinated' subgroups across MonumenTAL-1 and MajesTEC-1 may be more appropriate given that the company has access to individual patient data from both trials. The committee remained concerned with the likely impact of COVID-19 given that it was not a prognostic factor adjusted for in the company's original indirect treatment comparison. The committee also noted that a large proportion of deaths with teclistamab from MajesTEC-1 related to adverse events and infections. It considered the variability in how COVID-19-related deaths were recorded early in the COVID-19 pandemic and questioned whether some of the deaths caused by adverse events and infections were related to COVID-19. The committee

acknowledged that the company's indirect treatment comparison accounted for key prognostic variables. But it decided that the indirect comparison did not account for all relevant prognostic variables, particularly the impact of COVID-19. So, the committee concluded that a large amount of uncertainty remained.

Real-world evidence studies

3.9 At the first committee meeting, the EAG explored the overall survival and progression-free survival for talquetamab and teclistamab from MonumenTAL-1 and MajesTEC-1 by comparing these to published real-world evidence from Europe. The real-world studies included:

- one talquetamab study from Germany (Frenking et al. 2025; n=131)
- one teclistamab study from Germany (Riedhammer et al. 2024; n=122) and one from France (Perrot et al. 2025; n=312).

The EAG advised that these real-world studies showed superior overall survival and consistent progression-free survival compared with MajesTEC-1 for teclistamab and an inferior overall survival and progression-free survival compared with MonumenTAL-1 for talquetamab. The EAG explained that these studies likely included populations similar to UK NHS clinical practice, with its clinical advice suggesting that real-world evidence may better represent expected outcomes in UK practice.

In response to consultation, the company presented an indirect treatment comparison of talquetamab and teclistamab using 2 retrospective, non-interventional real-world studies, REALiTEC (teclistamab; n=113, median age=66 years) and REALiTAL (talquetamab; n=93, median age 65 years). These evaluated real-world outcomes in people with triple-class exposed relapsed or refractory multiple myeloma and included people from the UK. The company presented unadjusted overall-survival hazard ratios with and without subsequent-treatment adjustment. They also presented results using multivariable regression to control for differences in baseline characteristics and applied subsequent-treatment adjustment. The results of this analysis showed that talquetamab had an improvement in overall survival compared with teclistamab in all the scenarios. The hazard ratio for overall survival is

considered confidential by the company and cannot be reported here. The overall-survival hazard ratios in these analyses were all higher than the company's base case. The company explained that these analyses demonstrate that the results from MonumenTAL-1 and MajesTEC-1 are reflective of real-world clinical practice. The EAG noted that real-world evidence provides alternative overall-survival estimates to clinical trial evidence. But it said that all of the data is associated with limitations and so is unlikely to reduce the uncertainty in the overall-survival hazard ratio for talquetamab compared with teclistamab.

Committee conclusion on overall-survival hazard ratio

3.10 The committee recalled the high level of uncertainty associated with the overall-survival hazard ratio for talquetamab compared with teclistamab based on the company's indirect treatment comparison using MonumenTAL-1 and MajesTEC-1 data. It specifically recalled the:

- early separation of the talquetamab and teclistamab overall-survival curves (see section 3.6)
- lack of correlation between progression-free survival and overall survival, particularly the size of the overall-survival benefit (see section 3.7)
- impact of COVID-19 not being fully accounted for in the indirect treatment comparison (see section 3.8).

So, the committee decided that the overall-survival hazard ratio from the company's indirect treatment comparison was uncertain but likely overestimates the benefit of talquetamab. The committee also noted that the company's updated base-case hazard ratio did not include all pooled cohort-A and cohort-C data from MonumenTAL-1, which increased the hazard ratio. The committee also recalled that the company's indirect comparison using real-world studies resulted in a higher hazard ratio than in the base-case analysis (see section 3.9). The committee noted that both REALiTEC and REALiTAL were done after the COVID-19 pandemic and that the results of the indirect treatment comparison using these studies were not impacted by COVID-19. So, the committee decided that this analysis reduced some of the

uncertainty in the overall-survival hazard ratio. The committee noted that the overall-survival hazard ratio was likely to be higher than in the company's base case. It concluded that the broad range of overall-survival hazard ratio estimates from different analyses had helped to characterise the uncertainty. So, although there was still uncertainty in the estimates, the analyses helped the committee assess the impact of the different issues.

Economic model

Company's modelling approach

3.11 The company used a partitioned survival model with 3 health states: pre-progression, post-progression and death. The cycle length was 1 week and the time horizon was 40 years. The EAG was broadly satisfied with the company's model structure. It noted that the company discounted costs and quality-adjusted life years (QALYs) in the first year of the model and applied a half-cycle correction to account for mid-cycle transitions in the model. The EAG advised that discounting for costs and benefits in the first year was inappropriate. It also thought that the cycle length was not long enough to apply half-cycle corrections in the model. So, the EAG discounted costs and QALYs from year 2 onward and excluded the half-cycle correction in its base-case model. The committee noted that the company's model was similar to previous models used for multiple myeloma. At the first committee meeting, the committee decided the EAG's approach to discounting from year 2 onward and the exclusion of the half-cycle correction was appropriate. In response to consultation, the company updated its base-case economic model to include discounting for costs and benefits only from year 2 onward and exclude the half-cycle correction. The committee concluded that overall, the company's model structure was appropriate for decision making.

Long-term extrapolations of overall survival, progression-free survival and time to treatment discontinuation

3.12 To estimate long-term overall survival, progression-free survival and time to treatment discontinuation beyond the trial follow-up period, the company fitted parametric models to the MajesTEC-1 individual patient data for teclistamab. The company selected a log-normal model for all 3 outcomes and calibrated it to the clinical-expert estimates for these outcomes at 10 and 15 years in line with TA1015. The hazard ratios from the indirect treatment comparison for each outcome were then applied to the calibrated log-normal models for teclistamab. This was done to predict long-term overall survival, progression-free survival and time to treatment discontinuation for talquetamab. Long-term overall survival for talquetamab was then capped to the general population mortality. With differing hazard profiles for overall survival, progression-free survival and time to treatment discontinuation, the EAG noted that the same parametric model did not need to be selected for all 3 outcomes. It advised that extrapolating using the log-normal model produces implausible long-term overall-survival estimates. It said that in order to produce plausible overall-survival curves, the company had to force it into plausibility using clinical-expert estimates. The EAG also said that it did not think that the proportional-hazards assumption was compatible with the selected log-normal models. So, the EAG selected the Weibull model which does not need to be adjusted to produce clinically plausible estimates. The committee questioned the need to calibrate the log-normal models when there are other parametric models that would not need calibration. The company explained that selecting log-normal models for all 3 outcomes and calibrating them to meet clinical-expert estimates was consistent with the approach accepted by the committee in TA1015. The committee noted that individual patient data was available for both treatments. It said that using the IPTW method in the indirect treatment comparison would allow independent models to be fitted that would not need an assumption of proportional hazards. The committee thought that the EAG's approach using the uncalibrated Weibull model was more appropriate because it had not needed calibration. But it decided that it would prefer to see independent curves modelled rather than applying the indirect treatment comparison hazard ratios. At the first committee meeting, the committee concluded that it would like to see the long-term overall survival, progression-free survival and time to treatment discontinuation extrapolations modelled independently for both teclistamab and talquetamab without calibrating to the

clinical-expert estimates.

In response to consultation, the company updated its economic model. It independently modelled the long-term extrapolations of teclistamab and aligned them with the committee-preferred EAG approach by selecting the uncalibrated Weibull model across overall survival, progression-free survival and time to treatment discontinuation. But the company maintained that the hazard-ratio approach is more appropriate to derive these outcomes in the talquetamab arm instead of independently modelling them. So, it provided scenario analyses using independent modelling of long-term outcomes in the talquetamab arm using various parametric distributions. The company explained that the proportional-hazards assumption is valid and is associated with less uncertainty than independent modelling because it directly incorporates the results of the indirect treatment comparison. The EAG agreed with the company's hazard-ratio approach to modelling talquetamab outcomes. But it advised that the company's updated overall-survival hazard ratio used to model the long-term overall-survival outcomes was still associated with very high uncertainty (see sections 3.5 to 3.8). The committee acknowledged the uncertainty associated with the overall-survival hazard ratio from the indirect treatment comparison. But the committee concluded that independently modelling the long-term extrapolations in the teclistamab arm using the uncalibrated Weibull model was appropriate. It said that using the hazard-ratio approach to model long-term extrapolations in the talquetamab arm across overall survival, progression-free survival and time to treatment discontinuation was also appropriate.

Subsequent treatments

3.13 Some people in MonumenTAL-1 and MajesTEC-1 had subsequent treatments not routinely available in the NHS. To account for this, the company adjusted the overall-survival hazard ratio by removing the effects of these treatments using the 2-stage approach as per NICE Decision Support Unit's Technical Support Document 16. In its base case the company included subsequent teclistamab after talquetamab but excluded subsequent talquetamab after teclistamab. The EAG thought that the company's base-case approach was not equitable and did not allow for a fair comparison of talquetamab with teclistamab. The EAG explained that this approach affects both costs and QALYs and favours the

talquetamab arm. To allow for a fair comparison, in its base case, the EAG included both talquetamab and teclistamab as subsequent treatments after initial treatment. The clinical experts at the committee meeting noted that if talquetamab is recommended, some people will start talquetamab or teclistamab and then have the other treatment after disease progression. Whether to have treatment with talquetamab or teclistamab first would be a decision between a person with multiple myeloma and their healthcare practitioner. The committee noted the lack of detail in the company submission on how it adjusted for subsequent treatments not available in the NHS. It also noted that the company only used the Weibull model when adjusting for subsequent treatments using the 2-stage adjustment approach. The committee noted that other parametric distributions could have been explored in scenario analyses. At the first committee meeting, the committee concluded that:

- the costs and benefits of both subsequent talquetamab and subsequent teclistamab after initial treatment should be modelled
- it would like the company to provide a more detailed explanation of overall methods used to adjust for subsequent treatments not available in the NHS, and
- it would like to see analyses using parametric models, other than the Weibull model, when adjusting for subsequent treatments using the 2-stage adjustment approach.

  In response to consultation, the company included costs and benefits of both subsequent talquetamab and subsequent teclistamab in its updated economic model. It also provided additional methodological detail of the methods used to adjust for subsequent treatments not available in NHS clinical practice. And it provided scenario analyses using alternative parametric distributions for its 2-stage adjustment. The EAG agreed that the company's exploration of alternative parametric distributions and the proportional-hazards Weibull model were visually consistent with the company's original accelerated failure time Weibull model. It thought that this reduced uncertainty with the adjustment. The committee concluded that the company's accelerated failure time Weibull model was appropriate to adjust for subsequent treatments using the 2-stage adjustment approach.

Intravenous immunoglobulin use

3.14 People in MonumenTAL-1 and MajesTEC-1 could have intravenous immunoglobulin (IVIg) to prevent or treat infections. In the company's base-case analysis, IVIg use was modelled as a one-off cost in the first cycle in the talquetamab and teclistamab arms. This was in line with the observed IVIg use in the respective clinical trials. The proportion of people in the trials having IVIg is considered confidential and cannot be reported here. The company assumed 9 doses of IVIg in both treatment arms, which aligns with TA1015. The company noted that because of the novel G protein-coupled receptor class 5D target, people having talquetamab have less severe infections compared with teclistamab and so need less IVIg. The EAG thought that modelling IVIg use as a one-off cost underestimates IVIg costs in favour of talquetamab. It said that this is because it does not account for IVIg use by people having subsequent talquetamab and teclistamab after disease progression on the initial treatment. So, the EAG included IVIg costs associated with subsequent talquetamab and teclistamab in its base case. It based the proportion of IVIg use for subsequent talquetamab and subsequent teclistamab on the observed IVIg use in the respective clinical trials. These proportions are considered confidential and cannot be reported here. The EAG assumed 6 doses of IVIg for subsequent talquetamab and 9 doses of IVIg for subsequent teclistamab. The clinical experts said that there is a considerable difference in IVIg use between people having talquetamab and teclistamab in clinical practice. This is likely because there are fewer infections associated with talquetamab because of its novel target compared with teclistamab. The experts agreed that the proportions used in the company's base case are broadly reflective of NHS practice. The clinical experts also agreed that people having subsequent talquetamab and teclistamab would also need IVIg. At the first committee meeting, the committee decided that the proportion of IVIg use in the talquetamab arm based on MonumenTAL-1 and in the teclistamab arm based on MajesTEC-1 was appropriate. It also decided that IVIg use should be modelled for subsequent talquetamab and subsequent teclistamab.

In response to consultation, the company updated its economic model using the MonumenTAL-1 and MajesTEC-1 trials to inform the proportions of people having IVIg with talquetamab and teclistamab. The company also updated its economic model to include IVIg use for subsequent talquetamab and teclistamab, informed

by MonumenTAL-1 and MajesTEC-1. The committee concluded that the company's updated IVIg modelling, with the proportions having IVIg in the talquetamab arm being based on MonumenTAL-1 data and in the teclistamab arm being based on MajesTEC-1 data, was appropriate. It also concluded that basing IVIg use for subsequent talquetamab on MonumenTAL-1 data and basing IVIg for subsequent teclistamab on MajesTEC-1 data was appropriate.

Adverse-event disutilities

3.15 In its base case, the company applied a one-off utility decrement in the first cycle of the model for grade 3 or higher treatment-related adverse events. These events happened for at least 5% of people who had talquetamab or teclistamab. A higher utility decrement was applied in the teclistamab arm compared with the talquetamab arm because teclistamab was associated with more grade 3 or higher treatment-related adverse events. The EAG advised that including a utility decrement for adverse events may lead to double counting. This is because the effect of adverse events on health-related quality of life was likely captured in the patient-reported outcomes data collected in the trial, and this data was used to estimate the health-state utility values in the model. So, the EAG excluded modelling the utility decrement for adverse events separately to the health-state utility values. The patient experts explained that talquetamab is associated with altered taste in the first few months of starting it, which may result in subsequent weight loss. But the patient and clinical experts explained that these side effects are manageable, with weight loss being managed with dietitian support. A patient expert also explained that other treatments have more profound side effects, particularly fatigue and gastrointestinal side effects, which impact day-to-day life. The committee noted that altered taste and subsequent weight loss is likely to impact quality of life. But it noted that this had not been accounted for in the utility decrement applied for adverse events in the talquetamab arm because changes in taste are not classed as a grade-3 or 4 adverse event. The committee said that it would like the company to provide more explicit modelling of adverse-event disutilities and include the impact of altered taste and associated weight loss in the adverse-event disutility for talquetamab.

In response to consultation, the company provided further information on its modelling of adverse-event disutilities. It also included the impact of altered taste

and associated weight loss in its updated economic model. The committee concluded that the company's updated adverse-event disutilities modelling was appropriate for decision making.

Cost-effectiveness estimates

Acceptable ICER

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

- reduced clinical-effectiveness outcomes for cohort A in MonumenTAL-1 (see section 3.3)
- impact of COVID-19 on the clinical evidence (see section 3.8)
- indirect treatment comparison hazard ratio for overall survival (see sections 3.5 to 3.10), including the:
  - early separation of the talquetamab and teclistamab overall-survival curves (see section 3.6)
  - lack of correlation between progression-free survival and overall survival, particularly the size of the overall-survival benefit (see section 3.7)
  - impact of COVID-19 not being fully accounted for in the indirect treatment comparison (see section 3.8).

    The committee thought that there was considerable remaining uncertainty, especially in the magnitude of overall-survival benefit. But it decided that the introduction of real-world evidence and the company's

updated modelling of subsequent treatments, IVIg use and adverse-event disutilities had reduced some of this uncertainty. 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).

Company and EAG cost-effectiveness estimates

3.17 Because of confidential commercial arrangements for talquetamab, teclistamab and some of the subsequent treatments, the exact cost-effectiveness results are confidential and cannot be reported here.

Committee's preferred assumptions

3.18 The committee's preferred assumptions included:

- pooling data from cohort A and cohort C in MonumenTAL-1 to inform the clinical and cost effectiveness of talquetamab (see section 3.3)
- a range of overall-survival hazard ratios for talquetamab compared with teclistamab that were higher than the results of the company's indirect treatment comparison (see section 3.10)
- discounting for costs and QALYs from the second year of the economic model (see section 3.11)
- excluding half-cycle correction of costs and QALYs in the economic model (see section 3.11)
- independently modelling the long-term extrapolations in the teclistamab arm using the uncalibrated Weibull model and using the hazard-ratio approach to model long-term extrapolations in the talquetamab arm across overall survival, progression-free survival and time to treatment discontinuation (see section 3.12)
- including in the model the costs and benefits of using subsequent

talquetamab and subsequent teclistamab after initial treatment (see section 3.13)

- using the accelerated failure time Weibull model to adjust for subsequent treatments using the 2-stage adjustment approach (see section 3.13)
- the proportions having IVIg use in the talquetamab arm being based on MonumenTAL-1 data and in the teclistamab arm being based on MajesTEC-1 data, including subsequent talquetamab and teclistamab (see section 3.14)
- including the impact of altered taste and associated weight loss in the adverse-event disutility for talquetamab (see section 3.15).

The exact cost-effectiveness estimates using the committee's preferred assumptions cannot be reported here because there are confidential discounts for talquetamab, teclistamab and some of the subsequent treatments.

Other factors

Equality

3.19 A professional-organisation submission noted that there is an increased incidence of multiple myeloma and development of more severe disease in African and African-Caribbean people. People with more severe multiple myeloma are more likely to need additional lines of treatment because it is associated with an increased risk of relapse with earlier lines of treatment. Race is a protected characteristic under the Equality Act 2010. A patient organisation also said that as with all treatments the costs incurred by hospital visits and time off work will have a more significant impact on people with lower incomes. The committee decided that its recommendations do not restrict access to treatment for some people over others. So, the committee agreed that these were not potential equality issues in this evaluation. The committee did not identify any other equality issues.

Conclusion

Recommendation

3.20 The committee noted that the clinical-effectiveness evidence for talquetamab was uncertain, including the indirect comparison results for overall survival compared with teclistamab. But the cost-effectiveness estimates using its preferred modelling assumptions are within the range NICE considers a cost-effective use of NHS resources. So, talquetamab can be used.

4 Implementation

4.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 90 days of its date of publication.

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 routine commissioning, 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. Interim funding will end 90 days after positive final guidance is published (or 30 days in the case of drugs with an Early Access to Medicines Scheme designation or cost comparison evaluation), at which point funding will switch to routine commissioning budgets. 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 a NICE technology appraisal guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 60 days of the first publication of the final draft guidance.

4.4 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has relapsed and refractory multiple myeloma and the healthcare professional responsible for their care thinks that talquetamab is the right treatment, it should be available for use, in line with NICE's recommendations.

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 C.

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

Stephen O'Brien and Richard Nicholas
Chairs, technology appraisal committee C

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.

Zain Hussain
Technical lead

Claire Hawksworth and Alexandra Filby
Technical advisers

Leena Issa and Louise Jafferally

Project managers

Adam Brooke and Ross Dent
Principle technical adviser and associate director

ISBN: 978-1-4731-7423-8