NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final appraisal document

Ixazomib with lenalidomide and dexamethasone for treating relapsed or refractory multiple myeloma

1 Recommendations

1.1 Ixazomib, with lenalidomide and dexamethasone, is recommended as an option for treating multiple myeloma in adults, only if:

- they have had 2 or 3 lines of therapy and
- the company provides ixazomib according to the commercial arrangement (see section 2).

1.2 This recommendation is not intended to affect treatment with ixazomib that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

Why the committee made these recommendations

This appraisal reviews the additional evidence collected as part of the Cancer Drugs Fund managed access agreement for ixazomib with lenalidomide and dexamethasone (ixazomib combination) for treating relapsed or refractory multiple myeloma (NICE technology appraisal guidance 505). The original appraisal recommended ixazomib combination in people who have already had 2 or 3 lines of treatments. The usual treatment for these people is lenalidomide and dexamethasone.

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The new evidence includes data from a clinical trial and from people having ixazomib combination in the NHS while it was available in the Cancer Drugs Fund. The evidence suggests that people with multiple myeloma who have the treatment live longer compared with people who have lenalidomide and dexamethasone.

The cost-effectiveness estimates for ixazomib combination are likely to be within what NICE considers an acceptable use of NHS resources, so it is recommended.

2 Information about ixazomib

Marketing authorisation indication

2.1 Ixazomib citrate (Ninlaro, Takeda), in combination with lenalidomide and dexamethasone, is indicated for 'the treatment of adult patients with multiple myeloma who have had at least 1 previous therapy'.

Dosage in the marketing authorisation

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

Price

2.3 The list price is £6,336 per pack of 3 capsules (excluding VAT; BNF online, accessed November 2022).

2.4 The company has a commercial arrangement (simple discount patient access scheme). This makes ixazomib available to the NHS with a discount. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know the details of the discount.

3 Committee discussion

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

This review looks at data collected in the Cancer Drugs Fund to address uncertainties identified during the original appraisal. Further information about the original appraisal is in the committee papers. As a condition of the Cancer Drugs Fund funding and the managed access arrangement, the company was required to collect efficacy data from the TOURMALINE-MM1 (TMM1) study. Data was also collected using the Systemic Anti-Cancer Therapy (SACT) dataset.

The committee was aware that there were remaining areas of uncertainty associated with the analyses presented (see ERG report page 9) and took these into account in its decision making. It discussed the following issues, which were outstanding after the technical engagement stage:

- the company's Weibull models for overall survival appeared almost indistinguishable from the generalised gamma models
- uncertainty regarding the post-progression life-year gains in the adjusted overall-survival modelling
- the sustained effect of treatment when people have stopped taking the study treatments.

The condition and clinical management

Ixazomib combination is a valuable treatment option for people with relapsed or refractory multiple myeloma

3.1 Multiple myeloma is typically incurable and is a progressive disease that affects survival and quality of life. The patient experts explained that multiple myeloma causes debilitating symptoms including bone pain and bone fractures, tiredness, infections, hypercalcaemia (too much calcium in the blood) and kidney problems. The clinical experts noted that treating the disease becomes more and more challenging with each relapse. Treatment side effects and frequent hospital visits have an impact on people with multiple myeloma and their carers. The patient expert explained that ixazomib with lenalidomide and dexamethasone (ixazomib combination) has allowed them a long period of progression-free survival

and an improved quality of life with minimal side effects. The patient expert noted that they valued the oral administration of ixazomib combination. The committee considered the evidence from patient experts who have experience taking ixazomib combination and concluded that it is a valuable treatment option for people with relapsed or refractory multiple myeloma.

The population relevant to this appraisal is people who have had 2 or 3 previous therapies

3.2 Treatment options for multiple myeloma depend on a person's treatment history, their response to the treatments and their preferences. After 2 previous lines of treatment, options include lenalidomide plus dexamethasone, or panobinostat plus bortezomib and dexamethasone. After 3 previous lines of treatment, options include pomalidomide plus dexamethasone, or panobinostat plus bortezomib and dexamethasone. Daratumumab alone, and isatuximab with pomalidomide and dexamethasone are also available in the Cancer Drugs Fund. Ixazomib combination can be used after at least 1 previous therapy. The committee in the original appraisal (NICE technology appraisal guidance 505, from now referred to as TA505) understood that ixazomib combination would be used in the same place in the pathway that lenalidomide and dexamethasone is currently used; that is, for people who have had 2 or 3 previous therapies. The committee concluded that the population relevant to this review was people who have had 2 or 3 previous therapies.

Without ixazomib combination, there would be an unmet need for an oral triplet therapy for people who have had 2 or 3 previous therapies

3.3 The clinical experts explained that oral treatment regimens, which reduce pressure on hospital outpatient units and chemotherapy day units compared with intravenous options, are very important to people with multiple myeloma. They explained that oral treatment regimens reduce the risk of acquiring infections and that many people with multiple

myeloma are particularly concerned about contracting COVID-19 from hospitals. The clinical lead for the Cancer Drugs Fund explained that triple therapy is now standard at first and second line for people with multiple myeloma and that a fourth-line triplet therapy is available in the Cancer Drugs Fund. The patient expert explained that the benefits of ixazomib combination were not limited to the oral administration of the treatment, but also that it is a triplet therapy. The clinical lead for the Cancer Drugs Fund added that ixazomib combination has met the need for this preferred treatment option at third line. The committee concluded that, without ixazomib combination, there would be an unmet need for an oral triplet therapy for people who have had 2 or 3 previous therapies.

Lenalidomide plus dexamethasone remains the only relevant comparator

3.4 In TA505 the committee agreed that lenalidomide with dexamethasone was the relevant comparator. This was because, although the scope included bortezomib for people who have had at least 1 therapy, the committee for TA505 recalled that ixazomib combination was not expected to be widely used in people who have had 1 previous therapy. So, the committee in TA505 agreed bortezomib was not a relevant comparator. NICE guidance recommends both panobinostat plus bortezomib and dexamethasone, and lenalidomide plus dexamethasone after 2 previous lines of treatment. But the clinical experts in TA505 stated that they would always prefer to use lenalidomide before panobinostat, and therefore panobinostat is not used unless people have had 3 therapies or more. No changes to the scope are permitted in a Cancer Drugs Fund review and, in line with NICE's position statement on the consideration of products recommended for use in the Cancer Drugs Fund as comparators, treatments in the Cancer Drugs Fund cannot be considered comparators or included in the treatment sequence. So, the committee concluded that after 2 or 3 lines of treatment, lenalidomide plus dexamethasone remained the most relevant comparator.

Clinical-effectiveness evidence

Ixazomib combination improves progression-free survival after 2 or 3 lines of therapy

3.5 In TA505 the clinical-effectiveness evidence for ixazomib combination came from a second interim analysis data cut of TMM1, a phase 3 randomised controlled trial. The primary endpoint of the trial was progression-free survival. The median progression-free survival for ixazomib combination after 2 or 3 previous lines of treatment was 22 months compared with 13 months for lenalidomide and dexamethasone. The stratified hazard ratio was 0.62 (95% confidence interval [CI] 0.45 to 0.86, p=0.0033). This showed that ixazomib combination was associated with a statistically significant improvement in progression-free survival compared with lenalidomide and dexamethasone. The progression-free survival observations were not collected beyond the second interim analysis of TMM1 because this data was mature. So, the progression-free survival data was the same as the original appraisal. In TA505 the committee noted that the second interim analysis showed a reduced progression-free survival difference between arms compared with the first analysis, which was no longer statistically significant for the intention-to-treat population. However, it did remain significant for people who had had 2 or 3 previous therapies. The committee concluded that ixazomib combination improved progression-free survival in people who have had 2 or 3 lines of therapy.

The evidence from TMM1 is appropriate for decision making but has limitations

3.6 The committee in TA505 was concerned that the clinical benefit of ixazomib combination was uncertain because the overall-survival data was too immature to be considered robust. To address the committee's concerns from the original appraisal, the company provided the clinical-effectiveness for ixazomib combination from the final data cut of TMM1.

The trial included 722 people with relapsed or refractory multiple myeloma. A subgroup of 297 people, which included people who had had 2 or 3 previous lines of treatment, was relevant to this appraisal. The unadjusted median overall survival was 53 months for ixazomib combination and 43 months for lenalidomide and dexamethasone. The stratified hazard ratio was 0.85 (95% CI 0.64 to 1.11, p=0.232), showing ixazomib combination was not associated with a statistically significant improvement in overall survival compared with lenalidomide and dexamethasone. However, the clinical experts explained that overall survival is highly dependent on the choice of post-progression treatments. They further explained that the TMM1 trial had no UK centres, and the post-progression treatments would have varied depending on location and so were unlikely to be representative of UK practice. The company considered it was not appropriate to use the unadjusted overall-survival estimates from TMM1. The company explained that it had adjusted the data to remove the effect of subsequent therapies. This was because the treatment pathway in the trial did not reflect UK clinical practice and the distribution of subsequent treatments was not balanced between treatment arms (see section 3.8). The clinical experts noted that ixazomib is a proteasome inhibitor. They explained that because TMM1 was a blinded trial, some people whose disease progressed with ixazomib combination may have been given another proteasome inhibitor as a subsequent therapy. These people were likely to have been refractory to proteasome inhibitors at progression, so were given a potentially less effective treatment sequence than people in the lenalidomide and dexamethasone arm. The company did not adjust for this potential confounding, so, the committee heard that the overall-survival results were likely to be biased against ixazomib combination. The committee concluded that although the effect of ixazomib commination on overall survival in TMM1 was likely confounded by subsequent treatments, the data was acceptable for decision making.

Ixazomib likely improves overall survival

3.7 In line with NICE's position statement on the consideration of products recommended for use in the Cancer Drugs Fund as comparators, treatments recommended in the Cancer Drugs Fund cannot be considered comparators or subsequent treatments in NICE appraisals. NICE's guide to the methods of technology appraisal 2013 also advises that treatments not embedded in clinical practice in the NHS should not be considered as comparators or subsequent treatments. So, the company used the 2-stage method with recensoring to remove the effect of subsequent treatments from TMM1 not routinely used in the NHS, including those available via the Cancer Drugs Fund. The company assumed that the treatments removed in the 2-stage adjustment were effective and improved survival. The adjusted median overall survival was 51.4 months for ixazomib combination and 41.5 months for lenalidomide and dexamethasone. The stratified hazard ratio was 0.71 (95% CI 0.54 to 0.95, p=0.0216), showing ixazomib combination was associated with a statistically significant improvement in overall survival compared with lenalidomide and dexamethasone. The ERG explored additional analyses of the intention-to-treat population, including all 722 people, from TMM1. The ERG stated that in this population, which included people who had only had 1 previous line of treatment, the confidence intervals of overall survival crossed 1. The company highlighted that analysing this population was outside the scope of this review and it included people from a different treatment line who would have had different treatments and disease prognoses. The company also noted that a regional study of TMM1, in China, which did not face challenges of adjusting data for subsequent treatment therapies, showed a survival benefit with ixazomib combination. The committee concluded that an overall-survival benefit of ixazomib combination is likely.

Adjusting overall survival to remove the effect of subsequent treatments is appropriate

3.8 After adjustment for subsequent treatments, modelled post-progression life expectancy reduced to a greater extent in the lenalidomide and dexamethasone arm (a reduction of 0.3 life years) compared with the ixazomib combination arm (a reduction of 0.03 life years). The ERG noted that there were only small differences in the proportion of treatments not routinely used in the NHS or within the Cancer Drugs Fund in both treatment arms. Therefore, it was unclear why the reduction in life years was larger in the lenalidomide plus dexamethasone arm. The company explained that more people had treatments that extend survival in the lenalidomide and dexamethasone arm. The ERG also noted that modelled post-progression life-year gain, after adjustment, was 30.5% of the total life-year gain. Whereas, modelled post-progression life-year gain before adjustment was 7.4% of total life-year gain. The ERG stated that the change in life years gained departed from clinical plausibility. The company highlighted that there was a minimal difference between the cost-effectiveness estimates for the 2-stage method with recensoring and the unadjusted analysis. The committee noted these areas of uncertainty associated with the company's overall-survival adjustment, but was aware that using the adjusted analysis with recensoring versus unadjusted overall-survival data in the model made very little difference to the cost-effectiveness results. The committee concluded that although there was uncertainty about the adjustment to overall survival for subsequent treatments, the company's approach was appropriate.

Recensoring data in the 2-stage adjustment lowers the cost-effectiveness estimates

3.9 The committee noted that the company recensored the overall-survival data following its 2-stage adjustment, and that recensoring can overestimate the treatment effect. The committee considered that uncensored data should have been considered and that the cost-

effectiveness estimates were lower than they would have been if the company had not recensored the data. The company highlighted that the NICE Decision Support Unit technical support document 16 states that recensoring is required to avoid bias, particularly in cases where treatment switching is likely to be associated with prognosis, which was the case in TMM1. The committee concluded that the bias from recensoring the data was likely less than the bias from not censoring the data, but that the true cost-effectiveness estimates could be higher than the ones presented by the company.

There are differences between the population in TMM1 and the people eligible to have ixazomib combination in the NHS

3.10 NHS England also provided data from the SACT dataset. It was collected from 2,460 people who had ixazomib combination through the Cancer Drugs Fund between December 2017 and June 2020. The clinical experts explained that the clinical experience with ixazomib combination was positive. The clinical experts added that the SACT dataset shows that disease control and disease response with ixazomib combination was encouraging. The committee noted that the adjusted median overall survival in the trial was longer (51.4 months) than in the SACT dataset (30 months). Both the clinical experts and the clinical lead for the Cancer Drugs Fund explained that people included in the SACT dataset were older and had a poorer prognosis than people in TMM1. This may have contributed to the differences in the median survival estimates. The clinical experts added that the median follow up for overall survival was also shorter than the follow up in TMM1 and so not all benefits from ixazomib combination would have been captured. The committee recalled that the SACT dataset did not provide comparative evidence versus lenalidomide and dexamethasone and so a relative treatment effect from the use of ixazomib combination in the NHS could not be estimated. The committee agreed that the evidence from TMM1 was robust and the most appropriate for decision making. The committee concluded that population

differences likely contributed to the differences in treatment effects between TMM1 and the SACT dataset.

The company's economic model

The estimates of overall survival from each approach to modelling are similar

3.11 The company used data from the subgroup of people from TMM1 with relapsed and refractory multiple myeloma who had 2 or 3 previous lines of treatment. It used the generalised gamma model to estimate overall survival with ixazomib combination and lenalidomide and dexamethasone. It explained that it chose this model because its clinicians stated that the generalised gamma provided a reasonable estimation of long-term outcomes. The ERG proposed that the Weibull model was as valid on the grounds of clinical plausibility as the generalised gamma curve and was statistically better fitting than the generalised gamma model for both ixazomib combination and lenalidomide and dexamethasone. The clinical experts acknowledged that both the generalised gamma and Weibull curves estimated similar overall-survival outcomes. The clinical experts noted that survival seen in real-world practice in the NHS was much lower than the survival estimated by the parametric models. The company highlighted that there was a difference between clinical trial data and real-world data; in TMM1 around 35% of people were still alive after 8 years. The company added that people in clinical trials are often younger, have fewer comorbidities and have a better prognosis compared with people not in clinical trials. The committee concluded that although the generalised gamma curve was acceptable to extrapolate overall survival for ixazomib combination and lenalidomide and dexamethasone, the Weibull curve should also be considered.

The treatment waning effect is almost completely included in the trial follow up

3.12 In TA505 the company assumed that ixazomib combination's relative survival benefit in the clinical trial, compared with lenalidomide and dexamethasone, was maintained for the rest of a person's life after treatment stopped. The committee concluded in TA505 that, although it was biologically plausible for the relative treatment benefit to continue after stopping treatment, that level might not be maintained for the rest of a person's life. For this review, the company did not include a treatment waning effect in its base case. The company explained that the discontinuation of treatment had been almost completely captured within the 8-year observation time of TMM1. The company added that the hazard ratio or treatment effect in the ixazomib combination arm was a composite measure reflecting a pathway of treatments. The ERG agreed that the discontinuation and waning of treatment had been almost completely captured within the observed time of the trial, but noted that this was separate to the waning of the treatment effect. The ERG noted that over 90% of people were only observed for around 2 years following discontinuation of ixazomib combination. The ERG thought this was an insufficient time to capture any waning of treatment effect and conducted scenarios to explore the potential impact of treatment waning. The ERG did not include these scenarios in its base case. The ERG applied weighted hazards produced at each model cycle to generate an adjusted overall-survival estimate for people having ixazomib combination. Introducing a treatment waning effect increased the cost-effectiveness estimates of ixazomib combination. The committee recalled the long follow up of TMM1 and concluded that it largely captured the treatment waning and no other adjustments to treatment waning were needed.

The utility values used in the model are appropriate

3.13 In TA505 the committee recognised that the utility for progressed disease was higher than the UK population norms, and higher than in previous

multiple myeloma appraisals. In this review the company used updated EQ-5D data from TMM1. The ERG agreed that the utilities estimated from the final analysis of TMM1 better aligned with the literature and reflected the health-related quality of life of people with relapsed or refractory multiple myeloma. The committee concluded that the utility values used in the model were acceptable.

End of life

Ixazomib combination does not meet the end of life criteria

3.14 The committee considered the advice about life-extending treatments for people with a short life expectancy in NICE's guide to the methods of technology appraisal. In TA505 the committee considered that although ixazomib combination has the potential to improve overall survival, it did not meet the criterion for extension to life. The committee concluded that ixazomib combination could not be considered as an end of life therapy. The committee in this review concluded that its view from TA505 had not changed.

Cost effectiveness

The most likely cost-effectiveness estimates is below £30,000 per QALY gained

3.15 The committee preferred an analysis that included:

- either the generalised gamma or Weibull curve to extrapolate overall survival for ixazomib combination and lenalidomide and dexamethasone
- adjusted overall-survival modelling
- no additional treatment waning.

Using these preferred assumptions, the committee considered that the most plausible incremental cost-effectiveness ratio (ICER) for ixazomib combination compared with lenalidomide and dexamethasone was

below £30,000 per quality-adjusted life-year (QALY) gained. Because of confidential commercial arrangements for the treatments and comparators, the exact cost-effectiveness results cannot be reported here. The committee noted the level of uncertainty associated with the clinical- and cost-effectiveness results, specifically the adjusted and unadjusted estimates of overall survival and choice of model for extrapolating overall survival. But, it acknowledged that TMM1 was a robust study with a long follow up and mature data, and that this is rare in multiple myeloma. The committee commended the company on its efforts to present robust data. The committee also recognised the company's challenge to achieve cost-effectiveness for an add-on treatment to a combination therapy. The committee noted that the assumptions in the company and ERG base cases were very similar. It also recalled that there was a high level of unmet need for people with relapsed or refractory multiple myeloma at this line of treatment. The committee noted that people would welcome a new oral triplet therapy option for multiple myeloma at the third- and fourth-line treatment setting. The committee also noted the clinical need of this population, recalling the absence of an all-oral triple therapy at this point in the myeloma treatment pathway (see section 3.3). Taking these additional factors into consideration, the committee concluded that it was appropriate to recommend ixazomib combination for treating multiple myeloma after 2 or 3 therapies.

Equality issues

The recommendations apply equally to all people with relapsed or refractory multiple myeloma

3.16 Clinical experts noted that myeloma is twice as common in people of African-Caribbean family background. The committee considered that its recommendation applies equally, regardless of family background. It concluded that this difference in prevalence did not itself represent an equality issue in this appraisal.

Other factors

3.17 The clinical lead for the Cancer Drugs Fund highlighted that since December 2017, around 100 people per month who had previously had 2 or 3 lines of treatment have been able to have ixazomib combination through the Cancer Drugs Fund. The clinical experts explained that both clinicians and patients think ixazomib combination is a valuable treatment, as evidenced by the number of people having it. The patient experts noted that some of the treatments used to manage multiple myeloma involve injections and infusions and patients would welcome another oral treatment option. The committee acknowledged that the oral administration of ixazomib combination is a benefit, particularly for people who are older or frail, who find it difficult to travel to hospital for treatment. But the committee recalled that the main comparator, lenalidomide plus dexamethasone, is also an all-oral regimen. The clinical experts highlighted that ixazomib combination is the only oral triplet therapy for third-line treatments. The committee heard that this was an important treatment at this line of therapy, because triplet regiments are standard for people with multiple myeloma at first, second and fourth line. The patient expert described that people with multiple myeloma are often anxious about the COVID-19 pandemic, particularly because people with multiple myeloma are more at risk of severe infection and death. The clinical lead for the Cancer Drugs Fund added that because ixazomib combination is associated with longer progression-free survival compared with lenalidomide and dexamethasone, it delays the need for people to go into hospital. This reduces anxiety about hospital associated infections and the COVID-19 pandemic. The patient experts also noted that longer progression-free survival can be seen as a bridge to other future treatments that may be more effective. The committee concluded that ixazomib combination provides clinical benefit, in a population that has an unmet need for effective treatments, and that not all of the relevant benefits of ixazomib combination were captured in the modelling. The

committee considered these benefits qualitatively in determining an acceptable ICER (see section 3.15).

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 clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months 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 fast track appraisal), at which point funding will switch to routine commissioning budgets. The NHS England and NHS Improvement Cancer Drugs Fund list provides up-to-date information on all cancer treatments recommended by NICE since 2016. This includes whether they have received a marketing authorisation and been launched in the UK.

4.3 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document.

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 multiple myeloma after 2 or 3 lines of therapy and the doctor responsible for their care thinks that ixazomib combination is the right treatment, it should be available for use, in line with NICE's recommendations.

5 Appraisal committee members and NICE project team

Appraisal committee members

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

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

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

Chair

Megan John

Chair, technology appraisal committee D

NICE project team

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

Hannah Nicholas and Elizabeth Bell

Technical advisers

Kate Moore

Project manager

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