NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Ixazomib with lenalidomide and dexamethasone for relapsed or refractory multiple myeloma

The Department of Health has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using ixazomib with lenalidomide and dexamethasone in the NHS in England. The appraisal committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, clinical experts and patient experts.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the consultees and commentators for this appraisal and the public. This document should be read along with the evidence (see the committee papers).

The appraisal 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 race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The appraisal committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the committee will also consider comments made by people who are not consultees.
- After considering these comments, the committee will prepare the final appraisal determination.
- Subject to any appeal by consultees, the final appraisal determination may be used as the basis for NICE's guidance on using ixazomib in the NHS in England.

For further details, see NICE's guide to the processes of technology appraisal.

The key dates for this appraisal are:

Closing date for comments: 19 May 2017

Second appraisal committee meeting: 31 May 2017

Details of membership of the appraisal committee are given in section 5.

1 Recommendations

1.1 Ixazomib, with lenalidomide and dexamethasone, is not recommended within its marketing authorisation for treating multiple myeloma in adults who have already had at least 1 therapy.

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

Ixazomib (with lenalidomide and dexamethasone) has a marketing authorisation to treat multiple myeloma in people who have had 1 or more previous therapies, but it is likely to be used only for people who have had 2 or 3 previous therapies.

The main clinical trial is ongoing and limited data are available; it is not yet clear whether ixazomib prolongs life compared with the current treatment for people who have had 2 or 3 therapies (lenalidomide plus dexamethasone). In addition, ixazomib's benefit on the length of time people live without their disease progressing appeared to reduce after longer follow-up.

For people who have had 2 or 3 therapies, the minimum estimate of cost effectiveness varied between £138,000 and £176,000 per quality-adjusted life year (QALY) gained compared with current treatment. For people who have had 1 previous therapy, ixazomib was less effective than the current treatment (bortezomib plus dexamethasone) and cost more. Ixazomib was not recommended because it was not cost effective based on what NICE normally considers acceptable.

Ixazomib is not suitable for use within the Cancer Drugs Fund because it is unlikely to be cost effective at its current price even if the uncertainty about its effectiveness is reduced.

2 The technology

Ixazomib citrate (Ninlaro, Takeda)	
Marketing authorisation	'Ninlaro 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'.
Recommended dose and schedule	Capsules, 4 mg once a week on days 1, 8, and 15 of a 28-day cycle. Taken with lenalidomide 25 mg daily on days 1 to 21 of the cycle and dexamethasone 40 mg on days 1, 8, 15, and 22 of the cycle.
Price	£6,336 per cycle (3 capsules) (excluding VAT; NHS Dictionary of Medicines and Devices [accessed April 2017]). The company has agreed a patient access scheme with the Department of Health. If ixazomib had been recommended, this scheme would provide a simple discount to the list price of ixazomib with the discount applied at the point of purchase or invoice. The level of the discount is commercial in confidence. The Department of Health considered that this patient access scheme would not constitute an excessive administrative burden on the NHS.

3 Committee discussion

The appraisal committee (section 5) considered evidence submitted by Takeda and a review of this submission by the evidence review group (ERG). See the committee papers for full details of the evidence.

New treatment option

People with multiple myeloma will welcome a new treatment option

3.1 The patient experts explained that multiple myeloma is an incurable cancer characterised by multiple relapses, and patients would appreciate an additional option to extend the treatment pathway. The patient and clinical experts emphasised that oral treatment regimens are very

important, especially for elderly and frail patients. The committee concluded that people would welcome new oral treatment options for multiple myeloma.

Combining an immunomodulatory agent with a proteasome inhibitor is an important development in multiple myeloma treatment

3.2 The clinical experts explained that triple therapy regimens combining a proteasome inhibitor (such as ixazomib) with an immunomodulatory agent (such as lenalidomide) are becoming the standard of care for multiple myeloma. They explained that this is because of the synergistic effect of combining drugs with different mechanisms of action, which is particularly relevant later in the treatment pathway when multiple myeloma cells develop resistance to treatment. The clinical experts noted that the only triple therapy regimen currently available is bortezomib with thalidomide and dexamethasone, which is associated with severe side effects. The committee concluded that new triple therapy combinations with improved tolerability and more convenient administration would be welcomed.

People with multiple myeloma value longer periods between relapses

3.3 The patient expert explained that being progression-free is important to patients, both psychologically and physically. They also explained that a relapse of multiple myeloma, even without symptoms (known as biochemical progression), causes anxiety and affects daily activities. The patient expert noted that being progression-free means that the patient is free from the burden of treatment including having to travel, side effects and the unpleasantness of injections or infusions. The clinical experts noted that progression-free survival is an important outcome for patients because relapses can be fatal, especially in older people. The committee concluded that progression-free survival is important to people with multiple myeloma.

Clinical management

People who have had 1 previous treatment with bortezomib have limited treatment options

3.4 The committee understood that first-line treatment options for multiple myeloma differ depending on whether stem cell transplant is appropriate. Bortezomib plus dexamethasone, with or without thalidomide, is given as an induction therapy before stem cell transplant. If stem cell transplant is not suitable, thalidomide or bortezomib is offered (with melphalan and prednisone). The committee was aware that people who have had 1 treatment with thalidomide have bortezomib plus dexamethasone as second-line treatment. People who have had 1 treatment with bortezomib used to be offered retreatment with bortezomib or with lenalidomide plus dexamethasone through the Cancer Drugs Fund, but these are no longer available. The committee agreed that bortezomib retreatment, or lenalidomide plus dexamethasone, is not established practice in the NHS for people who have had 1 previous therapy. It noted that the NICE scope does not include any alternative treatment options. The committee heard from a clinical expert that there is a gap at this point in the treatment pathway and, because there are no alternative options, cytotoxic chemotherapy is offered (such as cyclophosphamide plus thalidomide and dexamethasone). However, there are no clinical data supporting cytotoxic chemotherapy at this point in the pathway. The committee concluded that people who have had 1 previous treatment with bortezomib have limited treatment options at first relapse.

Lenalidomide plus dexamethasone is used after 2 or 3 previous therapies

3.5 The clinical experts explained that, in current practice in England, lenalidomide plus dexamethasone is mainly used for people who have had 2 previous therapies. It can also be used for people who have had 3 previous therapies provided that they have not had lenalidomide before.

The committee noted that this was supported by market share data submitted by the company. These data showed that lenalidomide plus dexamethasone is the most common treatment for people who have had 2 previous therapies (69% of people) and that 25% of people who have had 3 or more previous therapies have lenalidomide. The clinical experts explained that many people in multiple myeloma clinical trials have not had lenalidomide as one of their 3 previous lines of therapy, and are therefore offered lenalidomide as their fourth treatment. The committee concluded that lenalidomide plus dexamethasone is established clinical practice for treating multiple myeloma in people who have had 2 or 3 previous therapies.

Panobinostat is mainly used only after 3 previous therapies

3.6 NICE's technology appraisal guidance on panobinostat for treating multiple myeloma recommends panobinostat plus bortezomib and dexamethasone for people who have had at least 2 previous therapies including bortezomib and an immunomodulatory agent. But the committee heard from the clinical experts that the panobinostat regimen is used later in the treatment pathway, because it is associated with toxic side effects and a complicated dosing regimen. The clinical experts 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. The committee heard from the clinical experts that panobinostat is sometimes reserved until later in the pathway, after 4 previous therapies, as an alternative to bendamustine. The committee concluded that the panobinostat regimen is mainly used only after 3 previous therapies.

Expected use of ixazomib

Ixazomib with lenalidomide and dexamethasone will be an alternative to lenalidomide plus dexamethasone

3.7 The company submission included analyses for people who have had 1 previous therapy and for people who have had 2 or 3 previous therapies. But the company expects ixazomib to be used mainly for people who have had only 2 previous therapies. The committee heard from the clinical experts that ixazomib (plus lenalidomide and dexamethasone) would be used in the same place in the pathway that lenalidomide plus dexamethasone is currently used; that is, for people who have had 2 or 3 previous therapies (see section 3.5). The committee agreed to consider the analysis in people who have had 1 previous therapy because it was part of the marketing authorisation, but concluded that the main population relevant to this appraisal is people who have had 2 or 3 previous therapies because this reflects the expected use of ixazomib.

Comparators

After 1 previous therapy, the comparator depends on the person's first treatment

3.8 The company submission included only 1 comparator for people who have had 1 previous therapy: bortezomib plus dexamethasone. The committee recalled that this comparator is only relevant for people who have had thalidomide, whereas for people who have had bortezomib the comparator is a cyclophosphamide-based regimen. The committee was aware that cyclophosphamide was not included as a comparator in the final scope from NICE, but noted that a comparison would not be possible because there are no data for cyclophosphamide in this population (see section 3.4). Additionally, the committee recalled that ixazomib is not expected to be widely used in people who have had 1 previous therapy. Because of this, the committee did not see any value in requesting a comparison with cyclophosphamide and NICE will not update and re-issue the scope. The committee concluded that bortezomib plus

dexamethasone is an appropriate comparator for people who have had 1 treatment with thalidomide.

After 2 previous therapies, the comparator is lenalidomide plus dexamethasone

3.9 The company submission included only 1 comparator for people who have had 2 previous therapies: lenalidomide plus dexamethasone. The committee agreed that this was appropriate and reflected clinical practice in England.

After 3 previous therapies, there are 2 comparators

3.10 The treatments available for people who have had 3 therapies are lenalidomide plus dexamethasone, or panobinostat with bortezomib and dexamethasone (see sections 3.5 and 3.6). The company submission included a comparison with lenalidomide plus dexamethasone for people who have had 2 or 3 previous therapies. The company explained that it did not provide a comparison with panobinostat because it expects ixazomib to be offered mainly to people who have had 2 previous therapies, instead of lenalidomide. The committee recalled that panobinostat is normally used after lenalidomide (see section 3.6) but concluded that it would have preferred to see a comparison of ixazomib with panobinostat for people who have had 3 previous therapies, in addition to the comparison with lenalidomide.

Clinical effectiveness

The clinical benefit of ixazomib is uncertain

3.11 The TOURMALINE-MM1 (TMM1) trial of ixazomib is ongoing. TMM1 is comparing ixazomib (plus lenalidomide and dexamethasone) against lenalidomide plus dexamethasone. The results of 2 interim analyses are available. The committee noted that median overall survival was not reached in either arm of the trial, and that the marketing authorisation for

ixazomib is conditional on the company providing additional clinical data, including more mature survival results. The clinical experts stated that they would expect to see a survival benefit with ixazomib after longer follow-up, but the committee agreed that the current data are too immature to make a reliable conclusion about overall survival. The committee noted that the difference between treatment arms in progression-free survival, the trial's primary end point, was statistically significant at the first interim analysis. But it was concerned that data from the second interim analysis showed a reduced progression-free survival difference between arms, which was no longer statistically significant for the intention-to-treat population. The committee noted that the benefit of ixazomib on other outcomes also reduced between the first and second interim analysis. The committee concluded that the clinical benefit of ixazomib is uncertain, based on the currently available data.

Ixazomib may be more effective after 3 previous therapies than after 2 previous therapies

3.12 TMM1 stratified patients according to the number of treatments they had before the trial, resulting in 2 pre-specified subgroups: people who have had 1 previous therapy and people who have had 2 or 3 previous therapies. The committee noted that the benefit of ixazomib in the subgroup who had 2 or 3 previous therapies appears to be driven by favourable results in the subgroup of patients who had 3 previous therapies, according to an analysis from the ERG of overall survival, progression-free survival and overall response rates. The committee noted a trend towards better hazard ratios in the 3 previous therapies subgroup than in the 2 previous therapies subgroup. The clinical experts expected the relative efficacy of ixazomib with lenalidomide and dexamethasone, compared with lenalidomide plus dexamethasone, to improve later in the treatment pathway. This is because triple therapy regimens are more effective than double therapy regimens in more

heavily pre-treated populations (see section 3.2). The committee concluded that there is a biologically plausible rationale for ixazomib to be more effective in the subgroup of people who have had 3 previous therapies.

Analyses after 3 previous therapies are uncertain

3.13 The company noted that it was inappropriate to consider the results from people who have had 3 previous therapies separately to the results from people who have had 2 previous therapies. This is because it breaks the randomisation of the trial, which was stratified according to number of previous therapies (1 and 2 or 3). The company explained that people who had 3 previous therapies had significant differences in prognostic baseline characteristics compared with people who had 2 previous therapies. It stated that the characteristics that differed may have artificially increased the treatment benefit seen with ixazomib in the subgroup of people who had 3 previous therapies. The committee acknowledged that this was a limitation of the ERG's analysis and a potential source of bias. However the committee concluded that if the company wants to make a case for using ixazomib only for people who have had 2 previous therapies then it would prefer to see analyses specific to this population, including some adjustment for differences in baseline characteristics. The committee acknowledged the potential limitations of this approach, but given the biological plausibility for differences in effectiveness (see section 3.12) it would have preferred to see an analysis in people who had only 2 previous therapies.

The company's network meta-analysis

The survival benefit of ixazomib is overestimated

3.14 The company did a network meta-analysis comparing ixazomib with lenalidomide and dexamethasone against bortezomib plus dexamethasone, in people who had 1 previous therapy. The results of the

company's analysis suggest that ixazomib improves overall survival compared with bortezomib, and that the difference between the 2 treatments is statistically significant (hazard ratio 0.31, 50% credible interval 0.13 to 0.65). The committee was aware that the ERG found an error in 1 of the inputs in the company's network for overall survival, which the company accepted in the meeting. This meant that the survival benefit of ixazomib was overestimated. The committee understood that the ERG had a number of other concerns about the company's methods and that it had done an exploratory network meta-analysis, which corrected the company's error and included alternative sources of efficacy data. The ERG's analysis of overall survival predicted a hazard ratio of 0.91 for ixazomib compared with bortezomib (95% confidence interval 0.43 to 1.92). The committee concluded that its decision-making should be informed by the ERG's network meta-analysis and not by the company's.

The company's economic model

The model should use the most recent clinical data

3.15 The company's base-case model used data from the first interim analysis of TMM1, and it provided a scenario analysis using data from the second interim analysis of the trial. The committee agreed that it would always prefer a company to include the most mature data in its economic model. The committee considered that this was particularly relevant for ixazomib, because the results differed between the first and second interim analyses. However, it noted that the ERG had several concerns about the validity of the company's scenario analysis using the most recent data from TMM1. The committee noted that the incremental cost-effectiveness ratio (ICER) for people who had 2 or 3 previous therapies decreased in the company's scenario analysis, but it was not sure what the true effect on the ICER would be if the ERG's concerns were addressed. The committee was not convinced that the analysis using data from the second interim analysis was robust. It concluded that it would have

preferred to see a model informed by the most recent clinical data for ixazomib, but that the model using the first interim analysis was acceptable for its decision-making.

Clinical evidence in the economic model

It is appropriate to use the data after 2 or 3 previous therapies to compare ixazomib with lenalidomide

3.16 The data in the model, for the comparison with lenalidomide plus dexamethasone, was based on people who had 2 or 3 previous therapies. The committee agreed that this was appropriate because both ixazomib and lenalidomide could be used for people who had 2 previous therapies and for those who had 3 previous therapies. However, recalling its discussions in sections 3.12 and 3.13, the committee preferred to see a scenario analysis in people who had 2 previous therapies only, adjusting for different baseline characteristics, to ensure that the average cost-effectiveness estimates across both subgroups (2 previous and 3 previous therapies) represent the cost-effectiveness estimates within the subgroups.

Effectiveness of bortezomib

The company's economic model underestimates the benefit of bortezomib for people who have had 1 previous therapy

3.17 The error in the company's network meta-analysis (see section 3.14) resulted in the company underestimating the overall survival benefit of bortezomib in its model. The company also used incorrect estimates of the distribution of best overall response with bortezomib in its model, which underestimated the pre-progression utility value for bortezomib. The company accepted these errors during the meeting. The committee concluded that it was more appropriate to use the ERG's exploratory network meta-analysis in the model analysis, and agreed with the ERG's

corrected estimates of the distribution of best overall response for bortezomib.

Health-related quality of life

The company's economic model overestimates the negative impact of injections

3.18 The company explained that it used published literature to estimate a utility decrement (that is, a reduction in health-related quality of life) for subcutaneous injections. The committee agreed that it is reasonable to associate inconvenient treatment regimens with a reduced quality of life. But it concluded that the company's estimate of −0.025 for subcutaneous bortezomib, applied for the full 3-week treatment cycle, was an overestimate.

It is unreasonable to assume better health-related quality of life after disease progression than for stable disease

3.19 The committee considered that the company's assumption of a higher utility value for progressed disease than for stable disease is clinically implausible, and heard from the ERG that it contradicts published literature. The clinical experts explained that they would not expect to see an immediate reduction in quality of life for people with progressed multiple myeloma. This is because disease progression is often diagnosed based on biochemical changes and people may not have symptoms of disease progression until weeks or months later. The committee acknowledged this, but noted that the model applies the same utility value for progressed disease until 3 months before death. The committee did not consider that this constant utility value was plausible because it heard from clinical experts that clinical progression (that is, symptoms of relapse) will always follow biochemical progression. The committee also recalled the patient expert's comments about the negative effect of both biochemical progression and clinical progression (see

section 3.3). The committee agreed that quality of life declines when a patient has clinical progression. It therefore concluded that the company had overestimated the utility value associated with progressed disease.

Utility estimates in the model are uncertain

3.20 The committee heard from the company that the results of its health-related quality of life analysis suggested that there was no interaction between quality of life and age or number of previous therapies. The committee considered it unlikely that age and treatment history have no effect on quality of life. It also noted the ERG's concerns that the pre-progression utility values may have been overestimated, because they were based on the best overall response of people in TMM1 rather than the response at the time that quality of life was assessed in the trial. The committee concluded that the utility estimates in the model were uncertain.

Costs

Extrapolating the duration of treatment data from the TMM1 trial underestimates treatment costs in the model

3.21 The ERG noted that there was a substantial difference between duration of treatment and progression-free survival in the company's model, when the estimates were extrapolated beyond the observed trial data. That is, patients stopped treatment before disease progression. Over the model's 25-year time horizon, people in the 2 or 3 previous therapies subgroup had ixazomib for only 65% of the time that they spent progression-free. In the lenalidomide arm, people had treatment for 75% of the time spent progression-free. The committee agreed with the ERG that this rate of stopping treatment before disease progression appeared higher than would be expected in practice, and considered it implausible that the ratio of time-on-treatment to progression-free-survival is lower for people having ixazomib than for people having lenalidomide. The committee also

noted that these ratios differed from those seen in TMM1, which the ERG noted were approximately 95 to 100%. The committee heard from the NHS commissioning expert that time-on-treatment is usually the preferred way to model treatment costs. But it understood that the company's method of analysing time-on-treatment was inconsistent with its methods for progression-free survival, which resulted in underestimated treatment costs. The committee concluded that extrapolating the duration of treatment data from TMM1 underestimates treatment costs in the model.

Costs of treatments taken after disease progression should be modelled weekly

3.22 The company applied a one-off cost for treatments taken after disease progression, assuming that 24% patients had such treatment. The committee and the company agreed with the ERG's correction to the number of people having subsequent treatment (41%). The committee agreed with the ERG that it is not appropriate to use a one-off cost to model treatments that are taken regularly, and concluded that treatments taken after progression should be modelled weekly.

The company's model overestimates the costs of bortezomib plus dexamethasone for people who have had 1 previous therapy

3.23 The committee agreed with the ERG's changes to the estimate of costs of bortezomib plus dexamethasone. It noted that the company had not properly implemented the treatment stopping rule and patient access scheme for bortezomib, which are part of NICE's technology appraisal guidance on bortezomib monotherapy, and was aware that the ERG was unable to explore the effect of including them. The committee therefore concluded that the cost of bortezomib was likely to be overestimated in the ERG's exploratory analyses.

Results (including patient access schemes)

Ixazomib is not recommended for people who have had 1 previous therapy

3.24 Because the company's model underestimated the benefit of bortezomib and overestimated its cost (see sections 3.17 and 3.23), the committee considered the results of the ERG's exploratory analyses. The committee noted that bortezomib plus dexamethasone dominated the ixazomib regimen (that is, bortezomib plus dexamethasone cost less and was more effective than ixazomib with lenalidomide and dexamethasone). Ixazomib cost around £169,000 more than bortezomib and was associated with around 0.4 fewer quality-adjusted life years (QALYs). The committee concluded that ixazomib with lenalidomide and dexamethasone could not be recommended as a cost-effective use of NHS resources for treating multiple myeloma in people who have had 1 previous therapy.

Ixazomib is not recommended for people who have had 2 or 3 previous therapies

3.25 The committee discussed the most plausible ICER for ixazomib in people who have had 2 or 3 previous therapies. It agreed with the changes in the ERG's alternative base case for this population, which increased the ICER slightly above the company's base-case estimate to £138,000 per QALY gained compared with lenalidomide plus dexamethasone. Ixazomib cost around £133,700 more than lenalidomide plus dexamethasone, and was associated with an additional 0.97 QALYs. The committee noted that the ICER increased when 2 of its preferred assumptions were incorporated in 2 separate sensitivity analyses:

- Increasing the cost of treatments taken after progression by applying weekly ongoing costs and increasing the proportion of patients having subsequent treatment increased the ICER to £151,000 per QALY gained, compared with lenalidomide plus dexamethasone.

- Using the extrapolation of progression-free survival to model treatment costs instead of time-on-treatment increased the ICER to £176,000 per QALY gained, compared with lenalidomide plus dexamethasone.

The committee noted that the ERG could not explore the effect of all of its preferred assumptions, such as utilities declining with age and line of treatment, which it considered would increase the ICER further. The committee concluded that ixazomib with lenalidomide and dexamethasone could not be recommended as a cost-effective use of NHS resources for treating multiple myeloma in people who have had 2 or 3 previous therapies.

The cost effectiveness of ixazomib compared with panobinostat, after 3 previous therapies, is uncertain

3.26 The committee would have preferred to see additional cost-effectiveness results for ixazomib compared with panobinostat, after concluding that panobinostat was an alternative option for people who have had 3 previous therapies, but the company did not provide this comparison. The committee's recommendation for people who have had 3 previous therapies was based on the comparison with lenalidomide plus dexamethasone in the combined population of people who have had 2 or 3 previous therapies.

End of life

Ixazomib does not meet the end-of-life criteria

3.27 The committee considered the advice about life-extending treatments for people with a short life expectancy in NICE's Cancer Drugs Fund technology appraisal process and methods. The committee focussed on the population who have had 2 or 3 previous therapies because this reflects the expected use of ixazomib. The committee also reasoned that if ixazomib did not meet the end-of-life criteria for this population, it would

not meet them for people with 1 prior therapy who have a longer life expectancy. The committee was aware that the company had not presented data to support considering ixazomib as an end-of-life therapy. It agreed that it could not make reliable conclusions about life expectancy and survival benefit using the results from TMM1, because the survival data are immature and the median overall survival was not reached in either arm of the trial. With that in mind the committee considered the estimates from the economic model, recognising that they were based on extrapolating immature data and were therefore uncertain. The committee discussed the criterion of short life expectancy with current treatment, which is normally less than 24 months, and noted that the modelled overall survival with lenalidomide plus dexamethasone was 3.6 years for people who have had 2 or 3 previous therapies. The committee therefore concluded that ixazomib does not meet the criterion of short life expectancy, and noted that this was consistent with the conclusions about life expectancy from other NICE technology appraisal guidance for people who have had 2 previous therapies. Although ixazomib did not meet the first end-of-life criterion, the committee discussed whether it has the potential to meet the criterion for extension to life, which is normally at least an additional 3 months. The committee considered that the modelled overall survival benefit and incremental QALY gain with ixazomib (see section 3.25) suggest that it has the potential to meet the criterion for extension to life, but agreed that these results were uncertain. The committee concluded that, based on the currently available data, ixazomib cannot be considered as an end-of-life therapy.

Cancer Drugs Fund

Ixazomib does not meet the criteria to be included in the Cancer Drugs Fund

3.28 The committee was aware that the company was interested in ixazomib being considered for the Cancer Drugs Fund. The committee discussed the new arrangements for the Cancer Drugs Fund agreed by NICE and

NHS England in 2016, noting the addendum to the NICE process and methods guides. The committee agreed that there is uncertainty about the clinical benefits of ixazomib, particularly for overall survival. It recognised that the survival data are immature and that median survival with ixazomib has not been reached in TMM1. It noted that additional survival analyses from TMM1 will be available by 2019, and that the final survival analyses from another study (the China continuation study) will be available in 2017. The committee noted that the company are required to collect these data, as well as data from a non-interventional observational study, as part of its conditional marketing authorisation.

3.29 The committee recalled its uncertainties about the progression-free survival benefit of ixazomib, which reduced after longer follow-up. It noted that there are no further planned analyses of progression-free survival in TMM1. However the committee noted that it had considered cost-effectiveness results based on the first interim analysis of TMM1, which was associated with more favourable progression-free survival than data from the second analysis.

3.30 The committee agreed that additional data collection has the potential to reduce the uncertainty about the clinical benefits of ixazomib. But it noted that the cost-effectiveness estimates are substantially above the range normally considered to be a cost-effective use of NHS resources, and did not consider it likely that reducing the clinical uncertainty would sufficiently reduce the ICERs. The committee did not see any plausible potential for ixazomib to satisfy the criteria for routine use at its current price.

3.31 The committee concluded that ixazomib does not meet the criteria to be included in the Cancer Drugs Fund.

Other factors

The committee did not identify any other factors that would affect its recommendations

3.32 No equality or social value judgement issues were identified.

3.33 The Pharmaceutical Price Regulation Scheme (2014) payment mechanism was not relevant in considering the cost effectiveness of ixazomib.

3.34 There were no additional health benefits that had not already been captured in the QALY calculations. The patient expert noted that most of the treatments used to manage multiple myeloma involve injections and infusions, therefore patients would welcome another oral treatment option. The committee acknowledged that the oral administration of ixazomib with lenalidomide and dexamethasone is a benefit, particularly for older or frail patients who find it difficult to travel to hospital for treatment. However the main comparator, lenalidomide plus dexamethasone, is also an all-oral regimen.

Conclusion

3.35 The committee could not recommend ixazomib, with lenalidomide and dexamethasone, for treating multiple myeloma in adults who have had at least 1 previous therapy.

4 Proposed date for review of guidance

4.1 NICE proposes that the guidance on this technology is considered for review by the guidance executive in December 2019. This review date reflects the deadline for Takeda to submit the results of new and ongoing studies to the European Medicines Agency, including the final overall survival analysis from the TMM1 trial. Providing these data is an obligation of the conditional marketing authorisation for ixazomib. NICE welcomes comment on this proposed date. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Gary McVeigh
Chair, appraisal committee
April 2017

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.

NICE project team

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

Sophie Cooper
Technical Lead

Raisa Sidhu
Technical Adviser

Kate Moore
Project Manager

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