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

Technology appraisal guidance
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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 are 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.

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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.
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1 Recommendations

1.1 Ixazomib, with lenalidomide and dexamethasone, is recommended for use within the Cancer Drugs Fund as an option for treating multiple myeloma in adults only if:

- they have already had 2 or 3 lines of therapy and
- the conditions in the managed access agreement for ixazomib are followed.

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 already had 1 or more lines of therapy. But it is likely to be used only for people who have already had 2 or 3 lines of therapy, for whom current treatment is lenalidomide plus dexamethasone, so the appraisal focused on this population.

The main clinical trial is ongoing. For people who have already had 2 or 3 lines of therapy, ixazomib (with lenalidomide and dexamethasone) increases the length of time they live without their disease progressing, when compared with lenalidomide plus dexamethasone alone. It is not yet clear whether ixazomib (with lenalidomide and dexamethasone) prolongs life compared with lenalidomide plus dexamethasone alone, but the initial results are promising.

Ixazomib does not meet NICE’s criteria to be considered a life-extending treatment at the end of life.

Ixazomib has the potential to be cost effective for people who have had 2 or 3 lines of therapy, at the price agreed in a commercial access agreement as part of the managed access agreement. But more evidence is needed to address the clinical uncertainties. It can therefore be recommended for use within the Cancer Drugs Fund while further data are collected from the clinical trial, and through the Systemic Anti-Cancer Therapy dataset.
2 Information about ixazomib

| Marketing authorisation indication | Ixazomib citrate (Ninlaro, Takeda), in combination with lenalidomide and dexamethasone, has a marketing authorisation for 'the treatment of adult patients with multiple myeloma who have had at least 1 previous therapy'. |
| Dosage in the marketing authorisation | Oral 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 November 2017]). As part of the managed access agreement, the company has a commercial access agreement with NHS England. This makes ixazomib available at a reduced cost. The financial terms of the agreement are commercial in confidence. |
3 Committee discussion

The appraisal committee (section 6) 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 that can be taken at home are very important, especially for older 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 international 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 becomes resistant to treatment. The clinical experts noted that the only available triple therapy regimen which combines a proteasome inhibitor with an immunomodulatory agent is bortezomib with thalidomide and dexamethasone, which is associated with severe side effects such as peripheral neuropathy. 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 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 line of bortezomib therapy have limited treatment options**

3.4 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 line of treatment with thalidomide have bortezomib plus dexamethasone as second-line treatment. People who have had 1 line of treatment with bortezomib used to be offered lenalidomide plus dexamethasone or retreatment with bortezomib, both 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 line of therapy. It noted that the NICE scope does not include any other treatment options as comparators. A clinical expert explained that there is a gap at this point in the treatment pathway and, because there are no other 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 line of treatment with bortezomib have limited treatment options at first relapse.

**Lenalidomide plus dexamethasone is used after 2 or 3 lines of therapy**

3.5 The clinical experts explained that, in current practice in England, lenalidomide plus dexamethasone is mainly used for people who have had 2 lines of therapy. It can also be used for people who have had 3 lines of therapy 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 used for 69% of people who have had 2 lines of therapy and 25% of people who have had 3 or more lines of therapy.
The clinical experts explained that many people in multiple myeloma clinical trials have not had lenalidomide as 1 of their 3 lines of therapy, and are therefore offered lenalidomide plus dexamethasone 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 lines of therapy.

**Panobinostat is mainly used only after 3 lines of therapy**

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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 lines of therapy including bortezomib and an immunomodulatory agent. But the clinical experts explained that the panobinostat regimen is used later in the treatment pathway, because it is associated with toxic side effects and a complicated dosing regimen. They stated that they would always prefer to use lenalidomide before panobinostat, and the company said that this was supported by market research data. Therefore panobinostat is not used unless people have had 3 lines of therapy. The clinical experts also explained that panobinostat is sometimes reserved until later in the pathway, after 4 lines of therapy, instead of bendamustine. The committee concluded that the panobinostat regimen is mainly used only after 3 lines of therapy, one of which usually includes lenalidomide.

**Expected use of ixazomib**

Ixazomib will be used mainly for people who have had 2 or 3 lines of therapy, instead of lenalidomide plus dexamethasone.

The company submission included analyses for people who have had 1 line of therapy and for people who have had 2 or 3 lines of therapy. The clinical experts explained 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 lines of therapy (see section 3.5). The committee noted uncertainties about the relevant comparators for people who have had 1 line of therapy:

- The company submission included only 1 comparator for people who have had 1 line of 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 (see section 3.4). A comparison with cyclophosphamide was not possible because there are no data for it in this population. Because of this, and advice from experts that ixazomib is not expected to be widely used in people who have had 1 line of therapy, NICE did not re-issue the scope to include cyclophosphamide as a comparator.

- A review of the NICE technology appraisal guidance on lenalidomide plus dexamethasone in this population is ongoing.

At its first meeting the committee agreed to consider the analysis in people who have had 1 line of therapy because this population is included in the marketing authorisation, and the company presented some evidence for it. But in response to consultation, the company stated that it did not wish to pursue a recommendation for this population because of the uncertainties about the comparators. The company did not include analyses for people who have had 1 line of therapy in the additional evidence it submitted after the first committee meeting. The committee concluded that it would focus its discussion on people who have had 2 or 3 lines of therapy because this reflects the expected use of ixazomib in clinical practice.

Comparators

After 2 or 3 lines of therapy, the comparator is lenalidomide plus dexamethasone

3.8 The company submission included a comparison with lenalidomide plus dexamethasone for people who have had 2 or 3 lines of therapy. The committee agreed that this was appropriate and reflected clinical practice in England. It was aware that panobinostat with bortezomib and dexamethasone is also an option for people who have had 3 lines of therapy, but recalled that panobinostat is normally used after lenalidomide (see section 3.6). Therefore, it understood that panobinostat would be used only after ixazomib (which is given with lenalidomide and dexamethasone). The committee concluded that it was not relevant to compare ixazomib with panobinostat.

Clinical effectiveness

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

3.9 The TOURMALINE-MM1 (TMM1) trial of ixazomib is ongoing. TMM1 is comparing ixazomib (plus lenalidomide and dexamethasone) with lenalidomide
plus dexamethasone. The trial stratified patients according to the number of
treatments they had before the trial, resulting in 2 pre-specified subgroups:
people who have had 1 line of therapy and people who have had 2 or 3 lines of
therapy. The results of 2 interim analyses are available. The company used the
results of the second interim analysis (the most recent) in its updated model,
submitted after consultation. The primary end point of TMM1 is progression-
free survival, which the committee acknowledged was an important outcome
for people with multiple myeloma (see section 3.3). In the intention-to-treat
population the benefit of ixazomib on progression-free survival, compared with
lenalidomide plus dexamethasone, reduced over time; the difference between
treatment arms was statistically significant at the first but not the second
interim analysis. But the committee noted that for people who have had 2 or
3 lines of therapy, the difference between treatment arms in median
progression-free survival was statistically significant in both interim analyses; at
the second interim analysis the difference was 9 months (p=0.003). It
understood from consultation responses that this difference was clinically
meaningful. The committee concluded that ixazomib improves progression-free
survival in people who have had 2 or 3 lines of therapy.

The survival benefit of ixazomib is uncertain

3.10 The committee noted that, for people who have had 2 or 3 lines of therapy,
median overall survival was not reached in either arm of TMM1 (hazard ratio
0.65; 95% confidence interval [CI] 0.41 to 1.02). It was aware of a regional
follow-up study of TMM1, done in China. This showed a survival benefit with
ixazomib; the median overall survival was 25.8 months in the ixazomib arm
compared with 11.2 months in the lenalidomide plus dexamethasone arm
(hazard ratio 0.30; 95% CI 0.15 to 0.61, p=0.0001). The committee was aware
that the ixazomib marketing authorisation is conditional on the company
providing additional clinical data, including more mature survival results from
TMM1. The clinical experts stated that they would expect to see a survival
benefit with ixazomib after longer follow-up, but the committee concluded that,
although the results were promising, the data are too immature to allow a
reliable conclusion to be drawn about the overall survival benefit.
Differences in prognostic patient characteristics explain why ixazomib appears to be more effective after 3 lines of therapy than after 2

3.11 At its first meeting, the committee concluded that the benefit of ixazomib in the subgroup of people who have had 2 or 3 lines of therapy might be driven by favourable results in the patients who have had 3 lines of therapy, noting the ERG analysis of overall survival, progression-free survival and overall response rates. The company had stated that it was inappropriate to consider the results from people who have had 3 lines of therapy separately to the results from people who have had 2 lines of therapy. This is because it breaks the randomisation of the trial, which was stratified according to the number of previous lines of therapy (1 and 2 or 3). The company explained that people who had 3 lines of therapy had major differences in prognostic baseline characteristics compared with people who had 2 lines of therapy, which may have artificially increased the treatment benefit seen with ixazomib in people who had 3 lines of therapy. The company provided evidence to support this during consultation, and the ERG agreed with the company’s explanation. The committee concluded that the differences in prognostic baseline characteristics explain why ixazomib appears to be more effective after 3 lines of therapy than after 2 lines of therapy, and it did not need to separately consider people who had 2 lines of therapy.

Clinical evidence in the economic model

It is appropriate to use data from after 2 or 3 lines of therapy to compare ixazomib with lenalidomide plus dexamethasone

3.12 The data in the model, for the comparison with lenalidomide plus dexamethasone, was based on people who had 2 or 3 lines of therapy. The committee agreed that this was appropriate because both ixazomib and lenalidomide plus dexamethasone could be used for people who have had 2 lines of therapy and for those who have had 3 lines of therapy.

Extrapolating clinical trial data in the economic model

Using a Weibull curve to extrapolate trial data predicts realistic long-term outcomes

3.13 In its original submission, the company extrapolated the observed data from TMM1 using a generalised gamma curve for progression-free survival, a Weibull
curve for overall survival and an exponential curve for time-on-treatment. The ERG was concerned that this produced clinically implausible results; for example, more people were alive with unprogressed disease than the total number of people alive, which is not possible. The committee discussed whether a Gompertz curve could be used to model overall survival, with a Weibull curve used for the other 2 outcomes. But consultees explained that the mortality rate predicted by a Gompertz curve was too high. In its updated model, the company used a Weibull curve to extrapolate all 3 outcomes (progression-free survival, overall survival and time-on-treatment). The ERG validated this approach by comparing the long-term survival estimates from the company's updated model with data from clinical trials of lenalidomide plus dexamethasone (MM-009 and MM-010), and trials of pomalidomide (MM-003 and STRATUS MM-010), in which the patient populations were similar to that in TMM1. The committee discussed the ERG's comments on the 5- and 10-year survival rates, post-progression survival, and the absolute estimate of post-progression survival. The committee agreed that the trial data supported using a Weibull curve for all 3 modelled outcomes. It acknowledged the ERG’s comment that the absolute post-progression survival estimate supported using the curves in the company’s original submission, but was aware that this approach resulted in a bigger difference between duration of treatment and progression-free survival than that seen in the trial on which the model’s outcomes were based. In TMM1 people had ixazomib for 92%, and lenalidomide for 97%, of the time spent progression free. In the company’s original submission, people in the 2 or 3 previous lines of therapy subgroup of the model had ixazomib for 62%, and lenalidomide for 69%, of the time spent progression free. These proportions increased to 92% and 100%, respectively, in the company’s updated model, which better reflected TMM1. On balance, the committee concluded that a Weibull curve should be used to extrapolate all 3 outcomes in the model: progression-free survival, overall survival and time-on-treatment.

**The continued treatment effect of ixazomib is unclear**

The company model assumed that the relative survival benefit of ixazomib in the clinical trial, compared with lenalidomide plus dexamethasone, was maintained at the same level after treatment stopped, for the rest of a patient’s life (that is, for 5.5 years with ixazomib and 3.9 years with lenalidomide plus dexamethasone, based on the modelled averages). The company justified its approach because the trial data supported the assumption of proportional
hazards. However, the committee noted that the proportional hazards assumption is proven for only the 23-month median trial follow-up period (that is, the relative benefit of ixazomib is constant for 23 months), and there is no evidence about what happens after this. The committee was aware that both the company and ERG had modelled alternative scenarios in which the treatment benefit in the extrapolated phase diminished in the long term, with several different assumptions about when the treatment effect starts to diminish and how quickly. The committee heard conflicting views from commentators, consultees and clinical experts about what happens after stopping ixazomib treatment. For example, 1 clinical expert stated that the relative benefit was likely to be maintained for at least 1 or 2 further relapses, diminishing over a period of about 2 years. Other clinical experts considered it reasonable to assume that the benefit of adding ixazomib to lenalidomide and dexamethasone continues for a patient’s lifetime. The committee agreed that although it was biologically plausible for the relative treatment benefit of ixazomib to continue after stopping treatment, it may not be maintained at the same level for the rest of a patient’s life. However, the committee acknowledged that it had not yet been presented with robust evidence to make a clear judgement on the duration of ixazomib's continued effect. On balance, the committee considered it was reasonable to consider the company’s base-case assumption about treatment effect in its decision-making.

Health-related quality of life

The company’s updated utility estimates are relevant to decision-making

3.15 The company’s updated model included a revised health-related quality-of-life analysis which adjusted for age, family origin, and sex. It also incorporated the response data from the time that quality of life was assessed in the trial. The updated analysis showed a reduced quality of life for progressed disease compared with stable disease, which the committee considered to be more plausible than the company’s original analysis. However, the ERG explained that the company had not accounted for the effect of prior or subsequent treatments on quality of life, which it considered to be implausible. The committee was also aware that the utility for progressed disease in the company’s updated model (0.751) was higher than UK population norms for this age group and higher than in previous appraisals on multiple myeloma, which the company and ERG were unable to explain. The committee acknowledged the
ERG’s concerns but concluded that, without any alternative utility estimates, the company’s updated utility analysis could be considered in its decision-making.

Costs

The costs of treatments taken after disease progression were underestimated in the ixazomib arm

3.16 The updated company model assumed that 66% of patients had further treatment after disease progression, based on data from the second interim analysis of TMM1. The ERG explained that the total cost of treatments taken after progression was the same in the ixazomib arm as in the lenalidomide plus dexamethasone arm, even though people having ixazomib lived for 26 weeks longer after stopping treatment than people having lenalidomide plus dexamethasone. The ERG suggested that this assumption was unrealistic because the number of post-progression treatments taken would be affected by how long a patient lives. The committee saw written statements from clinical experts supporting the ERG’s assumption. It was aware that the ERG had explored the impact of increasing the cost of post-progression treatments, but noted that the ERG’s assumptions were pessimistic. Therefore the committee did not consider the results of this scenario in its decision-making. It concluded that the model underestimated the cost of subsequent treatments in the ixazomib arm.

End of life

Ixazomib does not meet the end-of-life criteria

3.17 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, focusing on the population of people who have had 2 or 3 lines of therapy. The committee discussed the criterion of short life expectancy with current treatment, which is normally less than 24 months. It noted that the modelled overall survival of people who have had 2 or 3 lines of therapy taking lenalidomide plus dexamethasone was 3.9 years. The committee therefore concluded that ixazomib does not meet the criterion of short life expectancy. The committee acknowledged that this was based on uncertain model extrapolations, but noted that it was consistent with the conclusions.
about life expectancy from other NICE technology appraisal guidance for people with multiple myeloma who have had 2 lines of therapy. 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 (1.56 years) and incremental quality-adjusted life year (QALY) gain (0.97 QALYs) with ixazomib appeared promising, but agreed that these results were uncertain because most of the modelled improvement in survival occurred during the extrapolation of data beyond the trial period; 94% after the median follow-up period of 23 months, and 88% after the maximum follow-up of 32 months. The company stated that published literature suggests that progression-free survival is a good proxy for overall survival in multiple myeloma, but the committee was not aware of a validated measure to translate progression-free survival benefit into overall survival benefit. The committee was aware that the follow-up study from China showed a survival benefit with ixazomib (plus lenalidomide and dexamethasone) of 14.6 months for people who have had 2 or 3 lines of therapy. However, it was concerned that this was based on a small sample of patients outside the UK and would have preferred to see mature results from TMM1. The committee agreed that ixazomib has the potential to improve overall survival, but concluded that it did not meet the criterion for extension to life because the estimates were not sufficiently robust. The committee concluded that ixazomib cannot be considered as an end-of-life therapy.

**Cancer Drugs Fund**

**The company proposed ixazomib for the Cancer Drugs Fund**

3.18 The company requested the committee to consider ixazomib for the Cancer Drugs Fund rather than routine commissioning, for people who have had 2 or 3 lines of therapy, because of the uncertainty about the effect of ixazomib on overall survival. The committee recognised that the survival data were immature and that median survival with ixazomib had not been reached in TMM1. It noted that the final survival analysis from TMM1 will be available by 2019, with another interim analysis available in 2018. The committee understood that it was not considering ixazomib with lenalidomide and dexamethasone for routine use, and 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 company had proposed a confidential commercial access agreement for ixazomib within the Cancer Drugs Fund, and the committee considered the incremental cost-effectiveness ratios (ICERs) based on this commercial offer in its decision-making.

It is unlikely that ixazomib will satisfy the end-of-life criteria

3.19 The committee agreed that additional data collection has the potential to reduce the uncertainty about the overall survival benefit of ixazomib. So it considered whether there was plausible potential for ixazomib to meet the end-of-life criteria when more mature survival data are available. The committee recalled that the life expectancy of patients having lenalidomide plus dexamethasone in the model was 3.9 years, which exceeds the 24 months stated in the end-of-life criteria. The committee discussed whether it could apply its discretion by considering the proportional gain in survival compared with the prognosis based on the modelled estimates. However, life expectancy was substantially better than the 24 months stated in the end-of-life criteria, and the committee agreed that an extension to life of 1.56 years did not represent an exceptional proportional gain. The committee agreed that further data collection would reduce the uncertainty about the survival benefit of ixazomib, but did not see any plausible potential for ixazomib to satisfy the end-of-life criteria based on the current estimates of life expectancy and proportional survival gain with ixazomib.

Ixazomib is recommended for use within the Cancer Drugs Fund

3.20 The committee agreed with the changes in the company’s updated base case, which produced an ICER for ixazomib of £31,691 per QALY gained compared with lenalidomide plus dexamethasone, when the proposed commercial access agreement for ixazomib was applied. The ICER increased in scenarios in which the relative treatment benefit diminished over time but the committee could not be certain that any of these scenarios were realistic. It also recognised that the additional long-term survival data being collected in TMM1 would reduce the clinical uncertainty and allow for a more certain cost-effectiveness estimate. A very small improvement in the hazard ratio for overall survival (from 0.69 to 0.67) brought the ICER below £30,000 per QALY gained. The second interim analysis of TMM1 produced a hazard ratio of 0.65. Recalling the clinical experts’ comments about the benefits of triple therapy and the expectation that longer
follow-up of TMM1 would show a significant survival benefit, and noting the survival results from the China follow-up study (see section 3.10), the committee was satisfied that the clinical uncertainty in the model could be addressed by collecting data. It was also satisfied that when the commercial access agreement was applied, ixazomib had plausible potential to be cost effective for the subgroup of people who had had 2 or 3 lines of therapy and met the criteria for inclusion in the Cancer Drugs Fund. It recommended ixazomib, with lenalidomide and dexamethasone, for use within the Cancer Drugs Fund as an option for adults with multiple myeloma who have already had 2 or 3 lines of therapy, if the conditions in the managed access agreement are followed.

Other factors

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

3.21 No equality or social value judgement issues were identified.

3.22 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, so 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. It was aware that ixazomib is the first orally administered proteasome inhibitor. However the main comparator, lenalidomide plus dexamethasone, is also an oral regimen.
4 Implementation

4.1 When NICE recommends a treatment as an option for use within the Cancer Drugs Fund, NHS England will make it available according to the conditions in the managed access agreement. This means that, if a patient has multiple myeloma and has already had 2 or 3 lines of therapy, and the doctor responsible for their care thinks that ixazomib, with lenalidomide and dexamethasone, is the right treatment, it should be available for use, in line with NICE's recommendations and the Cancer Drugs Fund criteria in the managed access agreement. Further information can be found in NHS England's Appraisal and funding of cancer drugs from July 2016 (including the new Cancer Drugs Fund) – A new deal for patients, taxpayers and industry.

4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance when the drug or treatment, or other technology, is approved for use within the Cancer Drugs Fund. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, for use within the Cancer Drugs Fund, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal determination or agreement of a managed access agreement by the NHS in Wales, whichever is the latter.

4.3 Ixazomib, with lenalidomide and dexamethasone, has been recommended according to the conditions in the managed access agreement. As part of this, NHS England and Takeda have a commercial access agreement that makes ixazomib, with lenalidomide and dexamethasone, available to the NHS at a reduced cost. The financial terms of the agreement are commercial in confidence. Any enquiries from NHS organisations about the commercial access agreement should be directed to gb.commercial@takeda.com.
5 Recommendations for data collection

5.1 As a condition of the positive recommendation and the managed access agreement, the company is required to collect updated efficacy data from the TOURMALINE MM-1 clinical trial. Data on overall survival and time-on-treatment will be collected through other sources including the Systemic Anti-Cancer Therapy (SACT) dataset.
6 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.

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Accreditation

NICE accredited

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