Ixazomib for relapsed or refractory multiple myeloma: review from an Evidence Review Group on a NICE Single Technology Appraisal

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Abstract

Ixazomib is an oral proteasome inhibitor used in combination with lenalidomide plus dexamethasone (IXA-LEN-DEX) and licensed for relapsed or refractory multiple myeloma (RRMM). As part of a Single Technology Appraisal (STA ID807) undertaken by the National Institute of Health and Care Excellence (NICE) the Evidence Review Group (ERG) Warwick Evidence was invited to independently review the evidence submitted by the manufacturer of ixazomib, Takeda UK. The main source of clinical effectiveness data about IXA-LEN-DEX came from the Tourmaline-MM1 (TMM-1) randomised controlled trial (RCT) in which 771 RRMM patients received either IXA-LEN-DEX or placebo-LEN-DEX as their 2nd, 3rd or 4th line treatment. Takeda estimated the cost-effectiveness of IXA-LEN-DEX using a *de novo* partitioned-survival model with three health states (pre-progression, post-progression and dead) and in their first submission this model was used to estimate the cost-effectiveness of IXA-LEN-DEX versus bortezomib + dexamethasone (BORT-DEX) in 2nd line treatment, and of IXA-LEN-DEX versus LEN-DEX in 3rd line treatment. To estimate the relative clinical performance of IXA-LEN-DEX versus BORT-DEX Takeda conducted network meta-analyses (NMA) for important outcomes. The NMA for overall survival was found to be flawed in several respects, but mainly because a hazard ratio input for one of the studies in the network had been inverted resulting in a large inflation of the claimed superiority of IXA-LEN-DEX over BORT-DEX and a considerable overestimation of its cost effectiveness. In subsequent submissions Takeda withdrew 2nd line treatment as an option for IXA-LEN-DEX. The manufacturer's first submission comparing IXA-LEN-DEX versus LEN-DEX for 3rd line therapy employed TMM-1 data from 3rd and 4th line patients as proxy for a 3rd line population. The appraisal committee did not consider this reasonable because randomisation in TMM-1 was stratified according to one previous treatment and two or more (2+) previous treatments. A further deficiency was considered to be the manufacturer's use of interim survival data rather than the most mature data available.

A second submission from the company focussed on IXA-LEN-DEX versus LEN-DEX as 3rd or 4th line treatment (the 2+ previous lines population) and a new patient access scheme was introduced. Covariate modelling of survival outcomes was proposed using the most mature survival data. The ERG's main criticisms of the new evidence included: the utility associated with the pre-progression health state was overestimated, treatment costs of ixazomib were underestimated, survival models were still associated with great uncertainty leading to clinically implausible anomalies and highly variable incremental cost-effectiveness ratio (ICER) estimates, and the company had not explored a strong assumption that the survival

benefit of IXA-LEN-DEX over LEN-DEX would be fully maintained for a further 22 years beyond the observed data which encompassed only approximately 2.5 years observation. The appraisal committee remained unconvinced that ixazomib represented cost effective use of NHS resources.

Takeda's third submission offered new base case parametric models for survival outcomes, a new analysis of utilities, proposed a commercial access agreement, and reiterated its request that ixazomib be referred to the cancer drugs fund (CDF) for further investigation. In a brief critique of the third submission the ERG agreed that the selection of appropriate survival models was problematic and at the request of NICE investigated external sources of evidence regarding survival outcomes. The ERG considered that some cost and utility estimates in the submission may have remained biased in favour of ixazomib. As a result of their third appraisal meeting the committee judged that for the 2 / 3 prior therapy population, and at the price agreed in a commercial access agreement, ixazomib had the potential to be cost effective. It was referred to the CDF so that further data could accrue with the aim of diminishing the clinical uncertainties.

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Key points for decision makers:

- Ixazomib combined with lenalidomide and dexamethasone has been approved by the European Medicines Agency (EMA) for patients with multiple myeloma who had received at least one prior therapy based on positive outcomes on progression-free survival when compared to placebo with lenalidomide and dexamethasone. The data on overall survival are not sufficiently mature to draw any meaningful conclusions on this outcome measure.
- Ixazomib combined 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 previously received 2 or 3 lines of therapy and if the conditions in the managed access agreement for ixazomib have been followed.
- When the outcome estimates derived from network meta-analyses and appear clinically implausible it becomes doubly important that network meta-analysis input data be thoroughly scrutinised.
- When Kaplan Meier curves are immature there is considerable uncertainty around the overall survival (OS) and progression-free survival (PFS) estimates, and a partitioned survival model does not impose any functional relationship upon these estimates. The plausibility of OS and PFS extrapolations can be further assessed by examining the relative balance between pre-progression survival gain and post-progression survival gain, together with the balance between pre-progression survival and post-progression survival within each treatment strategy

1. Introduction

The National Institute for Health Care and Excellence (NICE) is an independent body responsible for appraising licensed medical interventions and issuing guidance on their use within the UK National Health Service (NHS). Recently, NICE has assessed many new pharmaceutical products within single technology appraisals (STA) in which the manufacturer of a particular technology submits evidence in support of the clinical and cost effective use of its product in one single indication. NICE commissioned an Evidence Review Group (ERG), in this case Warwick Evidence (University of Warwick) to independently critique both the clinical and economic evidence submitted by the product's sponsor. For NICE STA ID807, Takeda UK limited submitted evidence for the use of ixazomib in combination with lenalidomide plus dexamethasone (IXA-LEN-DEX) for the treatment of relapsed or refractory multiple myeloma (RRMM). This paper summarises the ERG's critique of Takeda's submissions to NICE [1] and provides a brief summary of the development of NICE guidance.

2. ERG critique of the Decision Problem defined by the company

Multiple myeloma (MM) is a rare progressive haematological malignancy characterized by accumulating clone(s) of plasma cells in the bone marrow [2]. It accounts for about 2% of all newly diagnosed cancer cases in the United Kingdom (UK) [3]. The diagnosis is mainly based on the presence of monoclonal immunoglobulin in serum or urine and plasma cell infiltration in the bone marrow resulting in osteolytic lesions associated with pain, fractures, swelling and bone degradation. The overproduction of immunoglobulin in MM cells leads to an increased proteasome activity, which plays an essential role in regulating protein turnover and maintaining homeostasis within cells. The identification of this pathway led to the development of several proteasome inhibitors (PIs) of which only ixazomib is administered orally. PIs disrupt protein turnover, causing the accumulation of protein that can lead to cell death.

Most MM patients eventually relapse after an initial therapy; patients may harbour multiple clones of MM cells and therefore may require further treatment. The choice of subsequent treatment depends on several factors including type of previous treatment, a new regimen's capacity to induce a good response, its tolerance, and its ease of administration. Targeting

several MM sub-clones at once is the rationale for using combination-therapies in MM. In recent years, a number of novel agents have become available including PIs (bortezomib, carfilzomib, ixazomib,), and Immunomodulatory drugs (IMIDs) thalidomide, lenalidomide, pomalidomide, but not all combinations of options are currently recommended within the NHS. To date, the therapies combining novel drugs with different mechanisms of action used within the UK are mainly limited to first line treatment of MM with bortezomib plus thalidomide combined with dexamethasone. In contrast to some other combination regimens, IXA-LEN-DEX is an all oral therapy and Takeda proposed that this represented a distinct advantage for RRMM patients and health service providers.

The company's major source of evidence was the Tourmaline MM1 (TMM-1) randomised controlled trial RCT [4] in which 771 RRMM patients received either IXA-LEN-DEX or placebo-LEN-DEX as their 2nd, 3rd or 4th line treatment. In their first submission the company located IXA-LEN-DEX as a 2nd or 3rd line therapy in the treatment pathway. This excluded patients who had already received three lines of therapy.

The comparators considered by the company were: a) bortezomib with dexamethasone (BORT-DEX) for 2nd line therapy and b) lenalidomide with dexamethasone (LEN-DEX) for 3rd line therapy. Thus, in 2nd line treatment the company excluded LEN-DEX as well as bortezomib monotherapy or bortezomib retreatment, as potential comparators. The manufacturer's reasons for 2nd line LEN-DEX exclusion were an interim negative ACD issued from NICE and its lack of funding under the cancer drugs fund (CDF). If IXA-LEN-DEX is positioned as a 2nd line agent, it appears illogical that LEN-DEX itself is not considered a comparator. Furthermore, the ERG's clinical advice was that LEN-DEX can sometimes be used in 2nd line in NHS practice; additionally Takeda itself noted that market share for LEN-DEX is appreciable (at ~26%) implying quite frequent use. However, these data may not have reflected the recent exclusion of 2nd line LEN from the CDF. The ERG considered exclusion of bortezomib monotherapy to be reasonable since it is very rarely used as a single agent. The company excluded bortezomib-retreatment on the grounds that it was not funded by NHS England, however the ERG's clinical advice was that some centres do employ this treatment while others do not. The company's selection of BORT-DEX as the only 2nd line comparator forced the use of indirect treatment comparisons, estimated using network meta-analysis (NMA), in comparing the relative merits of IXA-LEN-DEX versus

BORT-DEX, whereas if LEN-DEX had been the comparator, direct evidence from the manufacturer's own RCT could have been used.

For 3rd line treatment (first submissions) the company excluded panobinostat-bortezomib-dexamethasone (PAN-BORT-DEX) as a potential comparator on the grounds of its predominant use as a 4th line therapy. NICE recommends PAN-BORT-DEX for RRMM patients who have received at least 2 prior regimens including bortezomib and an IMID, thus in the ERG's opinion it represents a 3rd line option, and its exclusion was not justified.

3. Company's original submission and outcome following first appraisal committee.

3.1. Submitted Clinical Evidence and ERG critique

The company's literature search and systematic review identified 14 relevant studies. These studies provided data for input into network meta-analyses (NMAs) to indirectly estimate the relative clinical effectiveness of IXA-LEN-DEX versus BORT-DEX in 2nd line treatment.

The ERG considered that TMM-1 [4] was of good quality, with a low risk of bias in most domains. Progression free survival (PFS), estimated at the first interim analysis (median follow-up ~15 months), was the pre-specified primary outcome[1].
Pre-specified secondary endpoints included overall survival (OS), overall response rates (ORR) and health related quality of life.

In the entire TMM-1 population, the Hazard Ratio (HR) of PFS for ixazomib (first interim analysis at 15 months follow up) suggested a 26% reduction in risk (HR 0.74, 95% CI 0.5, 0.94; p=0.012), which led to marketing approval of ixazomib. At a later data cut (23 months median follow up) analysis showed a smaller treatment effect of 18% risk reduction (HR 0.82, 95% CI 0.67, 1.0; p=0.054). Thus an initially observed benefit in the 1st interim analysis did not persist through the 2nd interim analysis. This was one of the reasons for an initial

[1] PFS was defined as the time from the date of randomisation to the date of first documentation of disease progression, based on central laboratory results and International Myeloma Working Group (IMWG) criteria as evaluated by an independent review committee (IRC), or death due to any cause, whichever occurred first.

negative opinion provided by the CHMP for the marketing authorisation. However, the company argued that the more mature analysis was non-inferential (added as a late amendment of the study protocol), and that according to the pre-specified statistical analysis plan PFS benefit had been demonstrated. The Committee for Medicinal Products (CHMP) revised their initial opinion and decided in favour of market approval. The ERG noted that a statistically significant difference in PFS with immature data was followed by no statistically significant difference on PFS when more mature data were available.

The HR for OS in patients treated with ixazomib compared to those receiving placebo was similar in first (HR for death 0.90, 95% CI 0.62, 1.32) and second (HR 0.87, 95% CI 0.64, 1.18) interim analyses.

In the 1 prior therapy population (2nd line therapy), the TMM-1 trial showed no statistically significant benefit of ixazomib in PFS or in OS. In the 2+ prior population (3rd and 4th line therapy), the benefit of ixazomib was greater than in 2nd line in PFS. OS benefit with ixazomib requires confirmation with more mature data[2].

Consistent with the NICE scope, the company presented separate analyses according to the number of prior therapies (one prior or two/three prior therapies). As described above, Takeda selected BORT-DEX and not LEN-DEX as the comparator for 2nd line treatment and so undertook NMAs to determine if any relative benefit derived from use of IXA-LEN-DEX. The characteristics of the studies used in the company's NMA are summarised in Table 1 which also shows the indirect links required to compare IXA-LEN-DEX versus BORT-DEX. The ERG noticed from the NMA output that while LEN-DEX and BORT-DEX performed very similarly in PFS (HR 0.97 for BORT-DEX versus LEN-DEX) there was an apparently very large advantage for LEN-DEX over BORT-DEX with regard to OS (HR 2.9 for BORT-DEX versus LEN-DEX). Similarly, the indirect comparison of IXA-LEN-DEX vs BORT-DEX suggested a reduced risk of progression or death for IXA-LEN-DEX (HR PFS 0.72, 95%CrI 0.41, 1.19), while the suggested benefit on OS for IXA-LEN-DEX vs BORT-DEX (0.31, 95%CrI, 0.13, 0.65) was very large and appeared clinically implausible. According to the investigations of Cartier et al., 2015[5] on the relationship of PFS and OS HRs seen in 25

[2] HR values are not reported because these were marked as confidential by the Company at the time of the appraisal

RCTs of treatments for MM this difference was extraordinary and unexpected (Figure 1). The ERG therefore investigated if the OS performance of BORT-DEX suggested from the company's NMA-based economic modelling tallied with that observed in the four BORT-DEX studies the company input to its NMA. To do this the ERG employed published KM plots and the method of Guyot et al., 2012 [6] to reconstruct the individual participant data within the four studies and to develop parametric models. The results are summarised in Figure 2 and show a large discrepancy between the "observed" OS under BORT-DEX and the company's model which was derived by applying the NMA HR of 2.97 to an exponential model of OS for 2nd line patients in the LEN-DEX arm of the TMM-1 RCT (note that in TMM-1 69% of patients had already previously been treated with bortezomib).

The ERG identified a major error in the company's HR inputs for their OS NMA which accounts for the erroneous BORT-DEX vs LEN-DEX and BORT-DEX vs IXA-LEN-DEX results. In its OS NMA the Company's HR input for death with dexamethasone versus bortezomib was 0.57, while in fact, as reported in the APEX trial [7], 0.57 corresponded to the inverse HR for death for bortezomib versus dexamethasone.

Using the same methods as for OS the ERG similarly investigated whether the PFS performance of BORT-DEX suggested from the company's NMA modelling tallied with that observed in the four BORT-DEX studies the company input to its PFS NMA. The results (Figure 2) suggest that Takeda's model of PFS for BORT-DEX is overoptimistic. By apparently overestimating BORT-DEX PFS and underestimating BORT-DEX OS the company models squeeze the difference between OS and PFS (equivalent to post progression survival) to a relatively small proportion of OS when compared to that "observed" in BORT-DEX studies. The rather large proportion of survival seen after progression in the four primary studies testing the effectiveness of BORT-DEX may partly reflect the use of subsequent treatments after progression.

Following the identification of the error in the Company's NMA, the ERG undertook a number of exploratory analyses on the clinical effectiveness estimates for the indirect comparison of IXA-LEN-DEX with BORT-DEX. The ERG undertook random-effects network meta-analyses using the programs "network" in Stata [8]. In patients with at least one prior therapy, which was used as a proxy source for patients with one prior therapy, the

ERG's HR estimates for PFS and OS were 0.75 (95%CI 0.41, 1.38) and 0.91 (95%CI 0.43-1.92) respectively.

Examination of the company's NMAs revealed several deviations from common practice. Indeed, the ERG has identified several methodological flaws in the NMA, in particular focusing on the assumptions of homogeneity, similarity, and consistency.
The transitivity assumption was violated, since the distribution of population characteristics that are effect modifiers differ across the treatment comparisons of the network (Table 1). One such treatment effect modifier in the Company's NMAs is the number of prior therapies. While the TMM-1 trial included around 60% patients at the first relapse, the MM-009 [9] and MM-010 [10] studies included around 60-65% of patients with 2 prior therapies. The Dimopoulos 2015 [11] study selected patients from 3 RCTs and restricted their sample to only those with 1 prior therapy. Another threat to transitivity is the difference in doses for DEX 40 (different scheduling) in TMM-1 vs. 009/010 trials.

The indirect comparison (for OS, HR for risk of death) IXA-LEN-DEX with BORT-DEX was estimated through comparing the HR estimates for two indirect comparisons. A longer pathway of multiple intermediate indirect comparison steps used to derive the main indirect comparison leads to even greater uncertainties in the estimates. The more intermediate links which separate the indirectly compared treatments, the more unreliable this comparison becomes, through increasing the standard error of the effect estimate. As a result the validity of the OS-HR estimate for the indirect comparison IXA + LEN + DEX vs. BORT + DEX was questionable.

The NMA did not form any closed loops. Understandably, consistency between indirect and direct comparisons was not assessed. Indeed, this is one of the main limitations of the evidence provided in the NMAs of the manufacturer's submission owing to the inability to judge to what degree the statistical dimensions of the transitivity assumption were violated.

RCTs and observational studies were both included in the same NMA. In the PFS NMA the company used the observational study Montefusco et al., 2015 [12], which compared BORT-DEX + cyclophosphamide versus LEN-DEX + cyclophosphamide in order to connect the network between BORT-DEX and LEN-DEX.

These aspects, taken together with an incorrect HR input in the NMA for OS, seriously challenge the validity of the NMA results.

3.2. Submitted Cost-effectiveness evidence and ERG critique

The company developed a partitioned survival model with a weekly cycle length and a 25 year time horizon; there were three main health states: dead, alive pre-progression, alive post-progression. Those in pre-progression were further subdivided according to their Best Overall Response (BoR) which could be any one of three categories. The distribution between BoR states was treatment specific and assumed to apply to patients over their entire PFS.

3.2.1. Survival modelling:

The company used the HRs from the NMAs to generate estimates of life years gained under different treatments. To generate a survival curve for any treatment compared to LEN + DEX, Takeda took the NMA HR for the comparator versus LEN + DEX and applied this to covariate adjusted fits for the LEN + DEX arm of the TMM-1 trial (an exponential fit from 5 months for OS and a gamma fit for PFS). The LYG in pre- and post-progression for 'X' were estimated from the area under these newly generated OS and PFS curves. This procedure forces an exponential (OS) or gamma (PFS) curve shape on the comparator, but there is no a priori reason to expect that the observed curve for the comparator will conform to a distribution that fits a treatment regimen with differing mechanism of action. The resulting survival curves from this procedure may be implausible and/or bear little relationship to the observed curves found in published studies, as was the case here for BORT-DEX in 2nd line treatment.

In addition to suggesting IXA-LEN-DEX as a 2nd line treatment for RRMM, Takeda's first submission proposed IXA-LEN-DEX as an option for 3rd line therapy instead of LEN-DEX. For this analysis Takeda employed OS and PFS survival data from the TMM-1 trial. The issues with the use of more or less mature data have been discussed above.
The appraisal committee considered that the use of data was inappropriate and that the most mature data available should have been used for the analyses.

3.2.2. Cost-evaluation:

In their base case, the estimates of incremental cost-effectiveness ratio (ICER) by the Company are outside NICE norms for willingness to pay for both 2nd and 3rd line therapy. Because of flaws in the company's NMA, and taking into consideration other issues (e.g. disposition of BoR states in PFS, utility values, and post-treatment costing) the ERG considered the face validity of the ICERs to be poor, especially for the 2nd line indication.

Using the HRs obtained from the ERG's own NMA comparing IXA-LEN-DEX to BORT-DEX, the ERG concluded that IXA-LEN-DEX is dominated by BORT+DEX in patients with one prior therapy.

3.3. Outcome following first appraisal committee

At the first appraisal meeting (March, 2017), the Committee were not convinced that IXA-LEN-DEX if used in the NHS as 2nd line or 3rd line therapy for RRMM would represent good value for money. The committee was also not persuaded that entering IXA-LEN-DEX into the CDF would alleviate model uncertainty sufficiently to allow a reasonably robust estimate of an ICER for IXA-LEN-DEX in 2nd line or 3rd line therapies.

4. Company's subsequent submissions, ERG critique, and outcomes following appraisal committees

4.1. Second submission

Takeda's second submission dropped IXA-LEN-DEX as 2nd line and 3rd line therapy and re-positioned IXA-LEN-DEX as a 3rd or 4th line therapy, with LEN-DEX as the relevant comparator. In this second submission the submitted evidence came appropriately from patients who had received two or more previous therapies, furthermore the company now used the most mature data available from TMM-1 and introduced a patient access scheme (PAS) which considerably reduced the ICER estimate and improved the apparent cost effectiveness of IXA-LEN-DEX. Even with more mature data there remained considerable uncertainties regarding which, if any, parametric models of OS and PFS provided well-fitting models that in extrapolation generated clinically plausible scenarios for overall survival and for partitioning of survival between pre- and post-progression survival. Because the OS data

were so immature, it was impossible to establish best parametric models on the basis of information criteria (AIC BIC). The company assumed proportional hazards between LEN-DEX and IXA-LEN-DEX and selected gamma models for PFS and Weibull models for OS. Surprisingly the PFS gamma model for the 2+ prior population receiving IXA-LEN-DEX generated notably less progression than was seen for the gamma model previously selected by Takeda for the one prior population; the ERG considered that this may represent a clinically implausible scenario. A further difficulty arose in the extrapolation of the gamma PFS model for the 2+ prior population in that it eventually generated more live non-progressed patients than there were live patients predicted by the company's OS model. This situation was avoided if Weibull models were selected for both PFS and OS, however now the split between pre- and post-progression survival became heavily in favour of post-progression gain which again some might consider clinically implausible in a heavily pre-treated population. These difficulties mainly stem from the immaturity of the OS data, and should be alleviated somewhat with extended follow up. A major assumption in the company modelling was that the OS advantage for IXA-LEN-DEX over LEN-DEX calculated from data for the "observed" period of about 30 months would be maintained throughout the further 23 years of the economic model; the ERG suggested this could be an optimistic assumption. The ERG explored alternative assumptions about costs incurred by treatment and the Quality of Life decrement post-progression; these explorations tended to inflate the ICER estimate. The panobinostat regimen (PAN-BORT-DEX) was again excluded as a comparator.

At a second appraisal meeting (July, 2017) the committee remained unconvinced that IXA-LEN-DEX provided good value for money within the NHS, and was not persuaded that the drug should be made available via the CDF.

4.2. Third submission

A third submission from Takeda proposed that IXA-LEN-DEX be considered for the CDF. The company proposed a confidential Commercial Access Agreement (CAA) and made some further modifications to inputs to their economic model. At the request of NICE the ERG undertook analysis of potentially relevant information external to the TMM-1 trial for the purpose of gaining some independent estimates of the likely ten-year survival for RRMM patients receiving 3rd or 4th line treatment in TMM-1, and to gauge the relative contributions from pre- and post-progression survival. Takeda and NICE suggested Dimopoulos et al., 2014 as an external data source; in this publication PFS and OS were reported for LEN-DEX patients pooled from two RCTs (MM-010 and MM-009) [9, 10]. This study provided more patients (n=353) with longer follow up (5 years) than were available from TMM-1. The ERG analysed this study using the methods described above. A gamma model of OS provided the best fit and predicted 10 year OS of ~ 5% which corresponded reasonably well with the company's Weibull model of OS. Using a gamma model for OS and lognormal model for PFS the pre- post-progression split was approximately 0.47: 0.53 and mean OS about 3.7 years. As a proxy for post-progression survival the ERG also analysed data reported for 1097 patients (pooled from three studies) followed for about 4 years presented in the NICE pomalidomide-low dose dexamethasone appraisal (TA338)[13]. These patients would approximately correspond to TMM-1 patients who had progressed since we can assume that people progressing after IXA-LEN-DEX or LEN-DEX would be offered a subsequent line of treatment with pomalidomide-dexamethasone (POM+low dose DEX). Gamma models provided best fits for both PFS and OS and the latter predicted mean survival of about 1.61 years, moderately less than the 1.96 year estimate from the Dimopoulos analysis.

At a third appraisal meeting (October, 2017) the committee concluded that there were substantial uncertainties associated with estimates of survival of patients receiving IXA-LEN-DEX as 3rd or 4th line therapy and that under the proposed CAA in the CDF there was a reasonable expectation these might be resolved sufficiently to be able to gauge the cost-effectiveness of this treatment.

4.3. **Final outcome: NICE guidance**

NICE guidance [14] was issued February 7 2018 and was as follows: "*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*". Although licensed for treatment of patients who have received at least one previous therapy the Appraisal Committee believed ixazomib triple therapy is likely to be used "*only for people who have already had 2 or 3 lines of therapy*". In focussing on this population of myeloma patients the Committee considered that the ongoing TMM-1 RCT indicated that, relative to lenalidomide plus dexamethasone alone, ixazomib triple therapy increases the length of time patients live without disease progression; furthermore the committee judged that although there were promising interim results from TMM-1 it was not yet clear whether ixazomib triple therapy prolongs life. At the price agreed in a commercial access agreement the Committee concluded that Ixazomib triple therapy had the potential to be cost effective for the 2 or 3 prior population (ICER of £31,691/quality adjusted life years [QALY]) gained compared with lenalidomide plus dexamethasone alone), but that more evidence was required to reduce clinical uncertainties and that it could 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*".

5. Acknowledgements:

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6. Author Contributions:

Xavier Armoiry conducted the critique of clinical effectiveness evidence, co-ordinated the project, and undertook additional analyses (NMA).

Martin Connock conducted the critique of clinical effectiveness evidence and undertook additional analyses.

Alexander Tsertsvadze conducted the critique of clinical effectiveness evidence and the NMA.

Ewen Cummins conducted, reviewed and critiqued the cost-effectiveness evidence.

G.J. Melendez-Torres conducted the critique of clinical effectiveness evidence and the NMA.

Pam Royle conducted the critique of the company searches.

Aileen Clarke co-ordinated the project and provided comments on the report.

This summary has not been externally reviewed by PharmacoEconomics.

7. Compliance with Ethical Standards

7.1. Funding

This report was commissioned by the NIHR HTA Programme as project number ID807.

7.2. Conflicts of Interest

X.A.: none to declare

M.C.: none to declare

A.T.: none to declare

E.C.: none to declare

G.J.M.T.: none to declare

P.M.: none to declare

A.C.: none to declare

8. References

1. Ixazomib citrate in combination with lenalidomide and dexamethasone for relapsed refractory multiple myeloma: A Single Technology Appraisal. Warwick Evidence. 2017.
2. Armoiry X, Aulagner G, Facon T. Lenalidomide in the treatment of multiple myeloma: a review. J Clin Pharm Ther. 2008 Jun;33(3):219-26.
3. Haematological Malignancy Research Network (HMRN). Myeloma. 2017 21/02/2017]; Available from: https://www.hmrn.org/statistics/disorders/24
4. Moreau P, Masszi T, Grzasko N, Bahlis NJ, Hansson M, Pour L, et al. Oral Ixazomib, Lenalidomide, and Dexamethasone for Multiple Myeloma. The New England journal of medicine. 2016 Apr 28;374(17):1621-34.
5. Cartier S, Zhang B, Rosen VM, Zarotsky V, Bartlett JB, Mukhopadhyay P, et al. Relationship between treatment effects on progression-free survival and overall survival in multiple myeloma: a systematic review and meta-analysis of published clinical trial data. Oncology Research and Treatment. 2015;38(3):88-94.
6. Guyot P, Ades AE, Ouwens MJ, Welton NJ. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. BMC Med Res Methodol. 2012;12:9.

7. Richardson PG, Sonneveld P, Schuster MW, Irwin D, Stadtmauer EA, Facon T, et al. Bortezomib or high-dose dexamethasone for relapsed multiple myeloma. New England Journal of Medicine. 2005;352(24):2487-98.
8. White IR. Multivariate random-effects meta-analysis. Stata Journal. 2009;9(1):40-56.
9. Weber DM, Chen C, Niesvizky R, Wang M, Belch A, Stadtmauer EA, et al. Lenalidomide plus dexamethasone for relapsed multiple myeloma in North America. New England Journal of Medicine. 2007;357(21):2133-42.
10. Dimopoulos M, Spencer A, Attal M, Prince HM, Harousseau JL, Dmoszynska A, et al. Lenalidomide plus dexamethasone for relapsed or refractory multiple myeloma. New England Journal of Medicine. 2007 22 Nov;357(21):2123-32.
11. Dimopoulos MA, Orlowski RZ, Facon T, Sonneveld P, Anderson KC, Beksac M, et al. Retrospective matched-pairs analysis of bortezomib plus dexamethasone versus bortezomib monotherapy in relapsed multiple myeloma. Haematologica. 2015 Jan;100(1):100-6.
12. Montefusco V, Capecchi M, Galli M, Pezzatti S, Patriarca F, Gherlinzoni R, et al. Bortezomib versus lenalidomide in multiple myeloma patients at first relapse: first interim analysis of a phase III study. Abstract PO-334 15th International Myeloma Workshop. 2015.
13. National Institute for Health and Care Excellence. Pomalidomide for relapsed and refractory multiple myeloma previously treated with lenalidomide and bortezomib: Technology appraisal guidance [TA338]. 2015 03/01/2017]; Available from: https://www.nice.org.uk/guidance/ta338
14. National Institute for Health and Care Excellence. Ixazomib with lenalidomide and dexamethasone for treating relapsed or refractory multiple myeloma, technology appraisal guidance [TA505] 2018; Available from: https://www.nice.org.uk/guidance/ta505

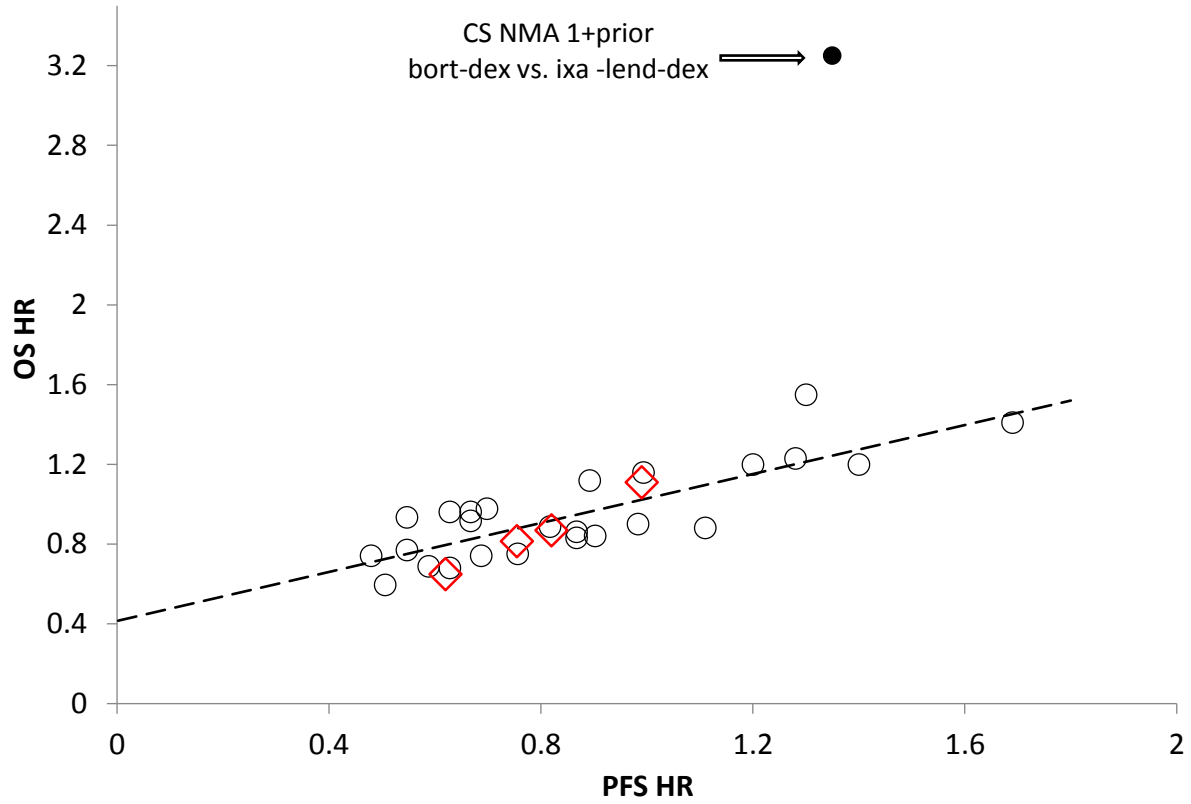

Figure 1 Relationship between PFS and OS HRs in RCTs of interventions for MM

Hollow circles = data digitised from Cartier et al. 2015. Diamonds = TMM-1 patients: all; 2'nd line, 3'rd line, and 3'rd or 4'th line. Solid circle = result from the Company's NMA. OS= overall survival; PFS= progression-free survival; HR= Hazard ratio; CS= company submission; NMA= network meta-analysis; bort-dex= bortezomib-dexamethasone; ixa-len-dex= ixazomib - lenalidomide – dexamethasone; 1+ prior= patients with at least one prior therapy

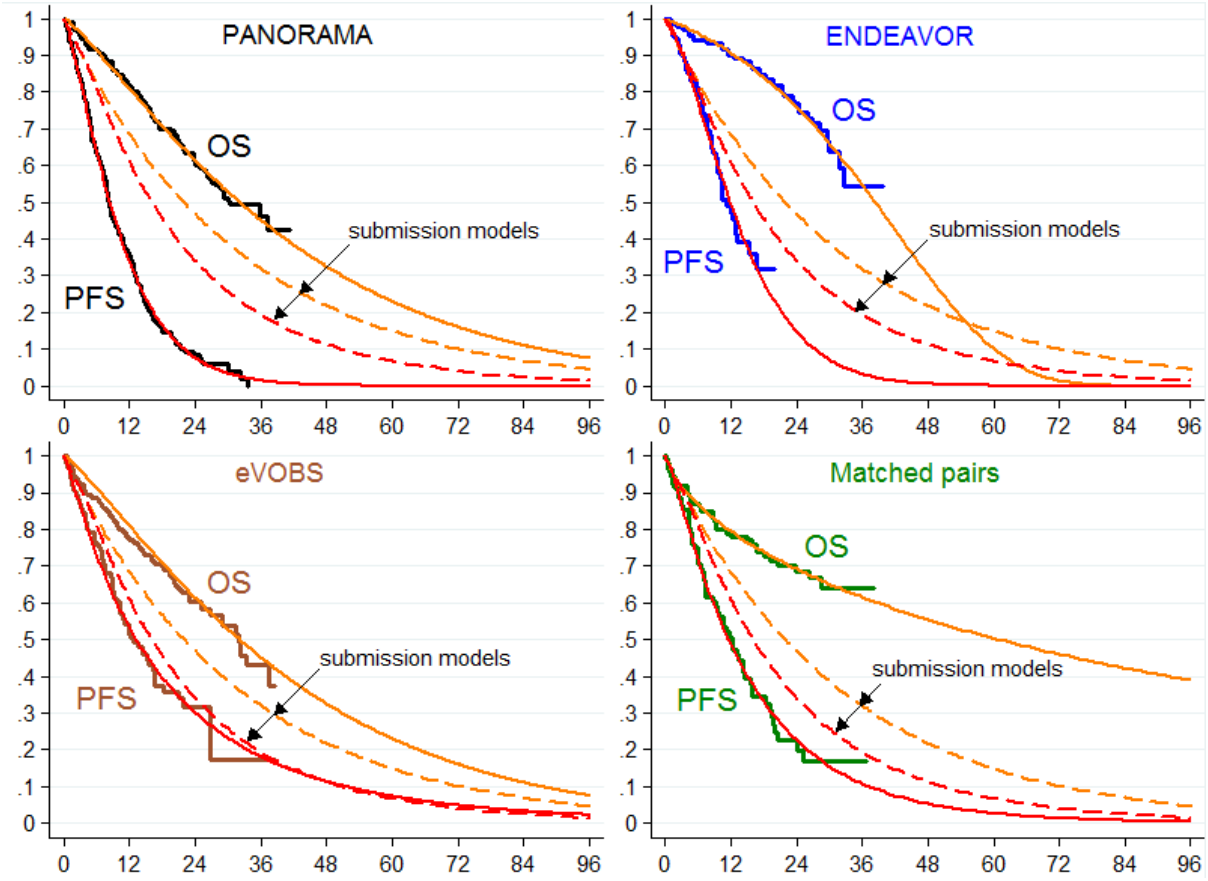

Figure 2 Kaplan Meier plots and parametric models (solid lines) of PFS and OS in BORT-DEX arms of trials included in the company's network meta-analysis, compared to the manufacturer's models for OS and PFS (dashed lines). *Note: the company's models of PFS and OS are less separated than seen in Kaplan Meier and parametric models of the NMA studies. OS= overall survival; PFS= progression-free survival;*

Table 1 Study characteristics of NMA studies used to link IXA-LEN-DEX to BORT-DEX

NMA PATHWAY LINKS	**IXA-LEN-DEX to LEN-DEX** ⇨		**LEN-DEX to DEX** ⇨				**DEX to BORT** ⇨		**BORT to BORT-DEX**	
Study names	**TMM 1 [4]**		**MM – 010 [10]**		**MM – 009 [9]**		**APEX [7]**		**Matched pairs RCTs [11]**	
Study arms (sample size)	IXA-LEN-DEX (N=360)	LEN-DEX (N=362)	LEN-DEX (N=176)	DEX (N=175)	LEN-DEX (N=177)	DEX (N=176)	DEX (N=336)	BORT (N=333)	BORT (N=109)	BORT-DEX (N=109)
Age, years, median (range) - yr	66 (38-91)	66(30-89)	63 (33-84)	64 (40-82)	64 (36-86)	62 (37-85)	61	62	64 (38-84)	62 (42-86)
Male sex - no (%)	207 (58)	202 (56)	(59.10)	(58.90)	(59.9)	(59.1)	200 (60)	118 (56)		
ECOG PS 0 no/total no (%)	180/354 (51)	170/358 (47)	78 (44.3)	65 (37.1)	74 (41.8)	83 (47.2)			25(23)	26 (24)
ECOG PS 1 no/total no (%)	156/354 (44)	164/358 (46)	72 (40.9)	79 (45.1)	83 (46.9)	80 (45.5)			73 (67)	71 (65)
Patients with 1 prior therapy -no. (%)	224(62)	217 (60)	56 (31.8)	57 (32.6)	68 (38.4)	67 (38.1)	119 (35)	132 (40)	109 (100)	109 (100)
Patients with 2 prior therapies -no. (%)	97 (27)	111(31)	120 (68.2)	118 (67.4)	109 (61.6)	109 (61.9)	194 (58)	186 (56)	0	0
Prior stem-cell transplantation	212 (59)	199 (55)	97 (55.1)	95 (54.3)	109 (61.6)	108 (61.4)	229/336 (68)	222/332 (67)	51 (57)	44 (40)
Prior bortezomib - no. (%)	248(69)	250 (69)	8 (4.5)	7 (4)	19 (10.7)	20 (11.4)	0%	0%	0%	(0)
Prior IMID therapy -no./ total no. (%)	193 / 360 (54)	204/362 (56)							38 (35)	45 (41)
Lenalidomide	44/360 (12)	44 /362 (12)	0%	0%	0%	0%	0%	0%		
Thalidomide	157/ 360 (44)	170/362 (47)	53 (30.1)	67 (38.3)	74 (41.8)	80 (45.5)	168/336 (50)	160/332 (48)		

BORT-DEX= bortezomib-dexamethasone; IXA-LEN-DEX= ixazomib - lenalidomide – dexamethasone; LEN-DEX= lenalidomide – dexamethasone; DEX= dexamethasone; ECOG= Eastern Cooperative Oncology Group; PS= performance status; IMID= Immunomodulatory drugs; NMA= network meta-analysis