

National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Ixazomib citrate in combination with lenalidomide and dexamethasone for relapsed or refractory multiple myeloma [ID807]

Response to consultee and commentator comments on the draft remit and draft scope

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Appropriateness	Leukaemia CARE	Yes	Thank you for your comment. No action required.
	Myeloma UK	<p>Myeloma UK considers this to be an appropriate topic to refer to NICE for a full appraisal.</p> <p>Proteasome inhibitors form the backbone of myeloma treatment in the UK and they are well-tolerated and highly effective. The opportunity for patients to have access to a very effective oral proteasome inhibitor will address an unmet need for patients, as it offers them the opportunity to avoid repeat and lengthy hospital appointments.</p> <p>We are pleased that NICE is making initial steps to appraise ixazomib for relapsed or refractory myeloma.</p>	Thank you for your comments. Ixazomib has been added to the NICE technology appraisals schedule.
	Takeda UK	Yes	Thank you for your comment.

Section	Consultee/ Commentator	Comments [sic]	Action
	UK Myeloma Forum	This is an appropriate and timely topic to refer to NICE for appraisal. Whilst myeloma can be controlled by some of the currently available treatments including the Lenalidomide / dexamethasone combination it will relapse in most patients. There is therefore a need to identify newer effective therapies that improve patient outcomes.	Thank you for your comments. Ixazomib has been added to the NICE technology appraisals schedule.
Wording	Leukaemia CARE	Yes	Thank you for your comment. No action required.
	Myeloma UK	We consider the draft wording of the appraisal to be accurate at this stage.	Thank you for your comment. No action required.
	Takeda UK	Yes	Thank you for your comment. No action required.
	UK Myeloma Forum	The technology does not currently have marketing authorisation. However, the wording of the remit reflects the presumed marketing authorisation based on known clinical trial publications. Please note that the Cancer Drugs Fund delisted 2nd line Lenalidomide on 4th November 2015.	Thank you for your comment. No action required. Thank you for comment. The background section of the scope has been updated to reflect this comment.
Timing Issues	Leukaemia CARE	-	

Section	Consultee/ Commentator	Comments [sic]	Action
	Myeloma UK	We consider this to be a timely appraisal of ixazomib. There are currently no oral proteasome inhibitors available on the NHS, so access is required to ixazomib as soon as possible.	Thank you for your comment. Ixazomib has been added to the NICE technology appraisals schedule, with consideration of the need to provide timely guidance.
	Takeda UK	No comment	Thank you for your comment. No action required
	UK Myeloma Forum	Almost all patients with myeloma will experience disease relapse with eventual development of drug resistance and eventual death. There is an urgent need for improved therapies for myeloma for administration either as monotherapy or in combination which are able to control the disease process for longer leading to extended life with maintained quality of life.	Thank you for your comments. Ixazomib has been added to the NICE technology appraisals schedule, with consideration of the need to provide timely guidance.
Additional comments on the draft remit	Leukaemia CARE	-	-
	Myeloma UK	It is important to note that there are a range of new treatments in the process of seeking a European license for relapsed and/or refractory myeloma, as similar setting to ixazomib. It is very important that NICE consider the myeloma clinical pathway of treatments in this, and other, appraisal(s) to ensure that it is logical and improves outcomes for patients.	Thank you for your comments. Ixazomib will be considered as a single technology appraisal, so that NICE can provide guidance

Section	Consultee/ Commentator	Comments [sic]	Action
			as soon as possible after a marketing authorisation is granted.
	Takeda UK	No comment.	Thank you for your comment. No action required.
	UK Myeloma Forum	The technology belongs to a class of drugs called proteasome inhibitors, that have proved to be very effective and life-extending drugs for the treatment of multiple myeloma. The only licensed proteasome inhibitors (bortezomib and carfilzomib) are given by subcutaneous or intravenous infusion, necessitating at least weekly, often twice weekly hospital visits. This technology is the first oral proteasome inhibitor to be licensed, and the impact on patient wellbeing and quality of life will be significant, given the older age and reduced mobility of this population. Thus this appraisal is urgent.	Thank you for your comments. Ixazomib has been added to the NICE technology appraisals schedule, with consideration of the need to provide timely guidance.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Leukaemia CARE	<p>The information in paragraph two is inaccurate. The draft scope states that “57% of people diagnosed aged 75 years and over” (referenced from CRUK). The correct information is that “43% of cases were diagnosed in people aged 75 years and over” (from CRUK).</p> <p>http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/myeloma/incidence#heading-One).</p> <p>Since the draft scope was written in October, lenalidomide has been delisted from the cancer drug fund.</p>	Thank you for your comments. The background section of the scope has been updated to reflect these comments.

Section	Consultee/ Commentator	Comments [sic]	Action
	Myeloma UK	<p data-bbox="696 300 1688 331">https://www.england.nhs.uk/wp-content/uploads/2015/11/ncdf-list-nov-15.pdf</p> <p data-bbox="696 360 1621 491">The background information needs to be updated to reflect the fact that Revlimid at first relapse (for myeloma patients previously treated with Velcade) has now been removed from the Cancer Drugs Fund in NHS England.</p> <p data-bbox="696 571 1688 737">Whilst NICE has issued a negative final appraisal determination (FAD) for Imnovid, it is routinely available in Wales for myeloma patients who have had at least two prior treatments including Velcade® (bortezomib) and Revlimid® (lenalidomide) and are refractory to their last line of treatment. Whilst it is not approved in England, this information is likely to affect the comparators.</p> <p data-bbox="696 759 1688 989">It might be useful to cover newly diagnosed NICE guidance for myeloma patients, to reflect that myeloma patients either have high-dose therapy and stem cell transplantation (with thalidomide or Velcade induction) or access thalidomide or Velcade through NICE MTA 228. Velcade retreatment is also being stopped in NHS England, which again is important information. This outlines the pathways of treatment for myeloma patients and is relevant to discussions at the scoping workshop.</p> <p data-bbox="696 1155 1688 1219">Also note that Velcade is always given in combination with dexamethasone at first relapse, not as a monotherapy.</p>	<p data-bbox="1733 360 2024 523">Thank you for your comments. The background section of the scope has been updated.</p> <p data-bbox="1733 580 2002 676">NICE technology appraisals guidance applies to England.</p> <p data-bbox="1733 766 2047 1101">Following discussion at the scoping workshop it was agreed that retreatment with bortezomib should be included as a comparator in the scope. The scope has been amended accordingly.</p> <p data-bbox="1733 1123 2047 1347">Following discussion at the scoping workshop it was agreed that botretzomib in combination with dexamethasone should be included as a</p>

Section	Consultee/ Commentator	Comments [sic]	Action
			comparator in the scope. The scope has been amended accordingly.
	Takeda UK	<p>Background statement third paragraph:</p> <p>“However, lenalidomide is available through the Cancer Drugs Fund for people with multiple myeloma who have received 1 previous therapy.”</p> <p>NHS England has announced the delisting of lenalidomide in this setting from the 4th November 2015.</p>	Thank you for your comments. The background section of the scope has been updated.
	UK Myeloma Forum	<p>This is largely accurate. It is also important to acknowledge the presence of NICE guidance for treatment of newly diagnosed patients as this will affect the treatments that can be offered according to NICE or the Cancer Drugs Fund at 1st, 2nd and 3rd line therapy. Currently newly diagnosed patients are treated according to whether they are transplant eligible or transplant ineligible depending on performance status and presence of medical comorbidities with younger, fitter patients generally considered to be transplant eligible.</p> <p>NICE TA311 is applicable to patients for whom stem cell transplant is planned and approves the use of bortezomib / dexamethasone or bortezomib / thalidomide / dexamethasone.</p> <p>NICE TA228 is applicable to non-transplant suitable patients and approves the use of alkylator therapy / thalidomide / corticosteroid or thalidomide substituted with bortezomib if thalidomide is contraindicated or not tolerated. Additionally, Bortezomib received approval for routine commissioning by NHSE in June 2013. This means that a significant proportion of patients will have already received a bortezomib based treatment prior to consideration of 2nd line therapy and beyond. In this case bortezomib as indicated by NICE as</p>	Thank you for your comments. The background section of the scope has been updated.

Section	Consultee/ Commentator	Comments [sic]	Action
		second line therapy is inappropriate for a proportion of patients (poor responders). In addition, the statement regarding 2nd line lenalidomide availability via the Cancer Drugs Fund is inaccurate following delisting in November 2015	
The technology/ intervention	Leukaemia CARE	-	-
	Myeloma UK	Myeloma UK considers this to be accurate.	Thank you for your comment. No action required.
	Takeda UK	The brand name of Ixazomib citrate is Ninlaro. The phase 3 randomised controlled trial of Ninlaro in combination with lenalidomide and dexamethasone is double-blind. This is different to most other trials in this setting which are open-label.	Thank you for your comments. The technology section of the scope has been amended.
	UK Myeloma Forum	Yes. The technology acts by inducing apoptosis via the disruption of protein handling and degradation pathways of proliferative tumour cells.	Thank you for your comments. No action required.
Population	Leukaemia CARE	Yes	Thank you for your comment. No action required.
	Myeloma UK	Myeloma UK considers this to be accurate, although discussion at the scoping workshop and subsequent clinical trial data may determine the best use for ixazomib in the clinical practice for relapsed myeloma patients.	Thank you for your comment. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
	Takeda UK	No comment.	Thank you for your comment. No action required
	UK Myeloma Forum	Yes.	Thank you for your comment. No action required.
Comparators	Leukaemia CARE	<p>As above, please note that lenalidomide has been delisted from the cancer drug fund. As such, it is only available in accordance with NICE TA 171.</p> <p>As listed in the scope, panobinostat is currently undergoing NICE appraisal and was not recommended in the recently published ACD. The anticipated publication date for panobinostat is January 2016. As such, the outcome of this appraisal (whether recommended or not) should be taken into account prior to the commencement of an appraisal for ixazomib citrate.</p>	Thank you for your comments. The background and comparator sections of the scope have been updated to reflect the number of previous therapies a patient has received and treatment options currently used in clinical practice in the NHS.
	Myeloma UK	<p>The comparators for the appraisal are correct, although panobinostat is not currently available at all for myeloma patients and the most appropriate setting to use this in has yet to be determined. Velcade and Revlimid are therefore the most appropriate comparators. Panobinostat is not available at all for patients in Wales.</p> <p>However, please note that Velcade retreatment is not a relevant comparator as this has been removed from NHS England commissioning and is not available to myeloma patients and in Wales retreatment is only available in exceptional circumstances through the individual patient treatment request</p>	Thank you for your comments. The comparator section of the scope has been updated to reflect the number of previous therapies a patient has received and treatment options currently used in clinical practice in the

Section	Consultee/ Commentator	Comments [sic]	Action
		<p>process.</p> <p>Imnovid (pomalidomide) for relapsed and refractory myeloma patients is approved as a treatment in Wales by the AWMSG. This should potentially be considered as a comparator for myeloma patients living in Wales.</p> <p>NHS England also funds bendamustine for the treatment of myeloma patients in the multiply relapsed setting. Whilst this may not be an appropriate treatment for all patients, it is worth discussing this as a potential comparator in the scoping workshop. Again, in Wales, this is only available in exceptional circumstances.</p>	NHS in England.
	Takeda UK	<p>Takeda UK anticipates that ixazomib citrate will be licenced in combination with lenalidomide and dexamethasone.</p> <p>Takeda UK note that the NICE Pathway for Multiple Myeloma states “Lenalidomide in combination with dexamethasone is recommended, within its licensed indication, as an option for the treatment of multiple myeloma only in people who have received 2 or more prior therapies”.</p> <p>Ixazomib citrate is therefore likely to fit into the NICE pathway as an addition to lenalidomide and dexamethasone in people who have received 2 or more prior therapies; i.e. in the third line setting.</p> <p>The NICE Pathway states that bortezomib is recommended as an option either “for the induction treatment of adults with previously untreated multiple myeloma, who are eligible for high-dose chemotherapy with haematopoietic stem cell transplantation” or “for the first-line treatment of multiple myeloma if high-dose chemotherapy with stem cell transplantation is considered inappropriate and the person is unable to tolerate or has contraindications to thalidomide”.</p> <p>On this basis, bortezomib (with or without dexamethasone) would not be considered a comparator in the third line setting (in people who have received</p>	Thank you for your comments. The comparator section of the scope has been updated to reflect the number of previous therapies a patient has received and treatment options currently used in clinical practice in the NHS.

Section	Consultee/ Commentator	Comments [sic]	Action
		<p>2 or more prior therapies).</p> <p>Takeda UK note that the NICE Pathway for multiple myeloma and the NHS England Cancer Drug Fund do not support re-treatment with bortezomib (it was delisted from the Cancer Drug Fund in January 2015).</p> <p>Takeda UK will take guidance from NICE on the status of “panobinostat with bortezomib and dexamethasone” and its relevance as a comparator in the third line setting.</p>	
	UK Myeloma Forum	<p>At 2nd line the most commonly used therapies are mainly Bortezomib based e.g. bortezomib / dexamethasone or cyclophosphamide / bortezomib / dexamethasone. Bortezomib monotherapy is rarely used due to inferior efficacy.</p> <p>At 3rd line Lenalidomide / dexamethasone as approved by NICE is the standard of care. Beyond 3rd line therapy bendamustine based treatment is the commonest approach, funded by the Cancer Drugs Fund.</p> <p>Panobinostat / bortezomib / dexamethasone has not been approved by NICE and would not be considered an appropriate comparator</p>	Thank you for your comments. The comparator section of the scope has been updated to reflect the number of previous therapies a patient has received and treatment options currently used in clinical practice in the NHS.
Outcomes	Leukaemia CARE	-	-
	Myeloma UK	We consider these to be the most important outcome measures for NICE to use in their appraisal.	Thank you for your comment. No action required.
	Takeda UK	Takeda UK note that “Time to next treatment” is not included in the TOURMALINE-MM1 clinical trial protocol. In addition to the other outcome measures listed in the Scope, the TOURMALINE-MM1 trial does collect data	Thank you for your comments. Attendees at the scoping

Section	Consultee/ Commentator	Comments [sic]	Action
		on the following parameters which may be useful surrogates: <ul style="list-style-type: none"> • Time to progression • Duration of response • Time to response. 	considered ‘time to next treatment’ was a clinically relevant outcome measure and therefore should remain in the scope. No action required.
	UK Myeloma Forum	Yes. Progression free survival as a surrogate for overall survival is an important outcome measure	Thank you for your comments. No action required.
Economic analysis	Leukaemia CARE	-	-
	Myeloma UK	No comment.	Thank you for your comment. No action required.
	Takeda UK	No comment.	Thank you for your comment. No action required.
	UK Myeloma Forum	Agree regarding appropriately long time horizon	Thank you for your comment. No action required.
Equality and Diversity	Leukaemia CARE	-	-
	Myeloma UK	No comment.	Thank you for your

Section	Consultee/ Commentator	Comments [sic]	Action
			comment. No action required.
	Takeda UK	No comment.	Thank you for your comment. No action required.
	UK Myeloma Forum	There are no equality issues for this therapy	Thank you for your comment. No action required.
Innovation	Leukaemia CARE	<ul style="list-style-type: none"> • Ixazomib citrate is the first oral proteasome inhibitor for the treatment of myeloma. • Granted accelerated assessment by the European Medicines Agency 	Thank you for your comment. The innovative nature of ixazomib citrate will be considered by the Appraisal Committee.
	Myeloma UK	<p>Myeloma UK considers this to be an effective and innovative treatment for relapsed or refractory myeloma. This is the first oral proteasome inhibitor which has the potential to impact significantly on the patient’s ability to live well with myeloma.</p> <p>In addition, the initial results of the Tourmaline-MM1 trial point to a significant extension of progression-free survival in patients that received Ixazomib, Revlimid and dexamethasone, compared to the standard Revlimid and dexamethasone arm.</p> <p>We look forward to seeing further results of the ixazomib trials which are likely to be published in the coming weeks.</p>	Thank you for your comments. The innovative nature of ixazomib citrate will be considered by the Appraisal Committee.
	Takeda UK	Ixazomib citrate is predicted to demonstrate a significant reduction in the risk	Thank you for your

Section	Consultee/ Commentator	Comments [sic]	Action
		<p>of progression and death versus the standard of care in the third line setting (in people who have received 2 or more prior therapies) via a sustained durable response.</p> <p>Ixazomib citrate is predicted to demonstrate a proven efficacy and sustained response across all patient groups including those in high unmet need and “difficult-to-treat” subgroups (including high-risk patients carrying deletion del(17), other high-risk cytogenetics e.g. t(4:14), t(14:16), elderly or frail patients) and regardless of prior treatment exposure.</p> <p>Ixazomib citrate is predicted to demonstrate a favourable toxicity profile enabling continuation of treatment and leading to a durable response.</p> <p>Ixazomib citrate is the first in class oral proteasome inhibitor that may enable efficiencies to the NHS healthcare care system particularly versus parenteral treatments currently available.</p> <p>Ixazomib citrate is a convenient once-weekly, single pill dose, and the all-oral combination with lenalidomide and dexamethasone reduces both patient and caregiver burden.</p>	<p>comments. The innovative nature of ixazomib citrate will be considered by the Appraisal Committee.</p>
	UK Myeloma Forum	<p>This is an innovative and effective therapy which is given orally. For the patient population this is would represent a significant improvement in terms of outcome and quality of life. The delivery of an oral therapy in this setting (if compared to e.g. bortezomib) would also have benefits in terms of reductions in hidden costs related to reduced chemotherapy unit attendance and pharmacy activity.</p>	<p>Thank you for your comments. The innovative nature of ixazomib citrate will be considered by the Appraisal Committee.</p>
Other considerations	Leukaemia CARE	-	-
	Myeloma UK	-	-

Section	Consultee/ Commentator	Comments [sic]	Action
	Takeda UK	-	-
	UK Myeloma Forum	Nil	Thank you for your comment. No action required.
Questions for consultation	Leukaemia CARE	-	-
	Myeloma UK	<p>As the trial is ongoing, the most appropriate place in the treatment pathway has yet to be fully established.</p> <p>Given that the large Phase III Tourmaline-MM1 trial is looking at ixazomib, Revlimid and dexamethasone compared to Revlimid and dexamethasone – it makes sense for discussion to centre around patients who have had two prior treatments. However, the interim results of the trial suggest that it is safe and effective in most stages of relapse. It is therefore important that a discussion is had at the scoping workshop as to where it fits in the pathway.</p> <p>It is not clear as to whether any subgroups of patients are likely to benefit more from ixazomib than others. However, it is important to consider the benefit of oral treatment combinations for certain groups of patients (i.e. patients who want to return to work or who are less able to attend hospital appointments).</p>	Thank you for your comments. No action required.
	Takeda UK	<p>Have all relevant comparators for ixazomib citrate been included in the scope?</p> <ul style="list-style-type: none"> Would panobinostat plus bortezomib and dexamethasone be a relevant comparator? <p>Takeda UK will take guidance from NICE on the status of “panobinostat with bortezomib and dexamethasone” and its relevance as a comparator in the</p>	Thank you for your comments. The

Section	Consultee/ Commentator	Comments [sic]	Action
		<p>third line setting, particularly following the removal of bortezomib retreatment from the Cancer Drugs Fund.</p> <p>• Which treatments are considered to be established clinical practice in the NHS for relapsed and refractory multiple myeloma?</p> <p>Takeda UK note that the NICE Pathway for Multiple Myeloma states “Lenalidomide in combination with dexamethasone is recommended, within its licensed indication, as an option for the treatment of multiple myeloma only in people who have received 2 or more prior therapies”.</p> <p>Ixazomib citrate is therefore likely to fit into the NICE pathway as an addition to lenalidomide and dexamethasone in people who have received 2 or more prior therapies; i.e. in the third line setting.</p> <p>Are there any subgroups of people in whom ixazomib citrate is expected to be more clinically effective and cost effective or other groups that should be examined separately?</p> <p>Ixazomib citrate is predicted to demonstrate a proven efficacy and sustained response across all patient groups including those in high unmet need and “difficult-to-treat” subgroups (including high-risk patients carrying deletion del(17), other high-risk cytogenetics e.g. t(4:14), t(14:16), elderly or frail</p>	<p>comparator section of the scope has been updated to reflect the number of previous therapies a patient has received and treatment options currently used in clinical practice in the NHS.</p> <p>The comparator section of the scope has been updated to reflect the number of previous therapies a patient has received treatment options currently used in clinical practice in the NHS.</p> <p>Thank you for your comment. No action required.</p>

Section	Consultee/ Commentator	Comments [sic]	Action
		<p>patients) and regardless of prior treatment exposure.</p> <p>Where do you consider ixazomib citrate will fit into the existing NICE pathway, Multiple myeloma?</p> <p>Takeda UK note that the NICE Pathway for Multiple Myeloma states “Lenalidomide in combination with dexamethasone is recommended, within its licensed indication, as an option for the treatment of multiple myeloma only in people who have received 2 or more prior therapies”.</p> <p>Ixazomib citrate is therefore likely to fit into the NICE pathway as an addition to lenalidomide and dexamethasone in people who have received 2 or more prior therapies; i.e. in the third line setting.</p>	<p>Thank you for your comments. The NICE pathway will be reviewed following publication of the guidance.</p>
	UK Myeloma Forum	<p>Panobinostat / bortezomib / dexamethasone would only be an appropriate comparator if approved for 2nd line therapy by NICE.</p> <p>It is likely that the technology would fit into the current NICE pathway either at 2nd line or 3rd line</p>	<p>Thank you for your comments. The comparator section of the scope has been updated to reflect the number of previous therapies a patient has received and treatment options currently used in clinical practice in the NHS.</p> <p>Thank you for your comment. The NICE pathway will be reviewed following</p>

Section	Consultee/ Commentator	Comments [sic]	Action
			publication of the guidance.
Additional comments on the draft scope	Leukaemia CARE	-	-
	Myeloma UK	-	-
	Takeda UK	No comment.	Thank you for your comment. No action required.
	UK Myeloma Forum	-	-

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

Department of Health