National Institute for Health and Care Excellence

Health Technology Evaluation

Selinexor with dexamethasone for treating relapsed or refractory multiple myeloma [ID6193]
Response to stakeholder organisation comments on the draft remit and draft scope

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Comment 1: the draft remit and proposed process

Section	Stakeholder	Comments [sic]	Action
Appropriateness of an evaluation and proposed evaluation route	Menarini-Stemline	Yes, this topic is appropriate for a NICE appraisal.	Thank you for your comment. No action required.
	Myeloma UK	Yes, this topic would be appropriate for a NICE appraisal. Myeloma is a relapsing and remitting, incurable cancer, and even after successful treatment, almost all patients eventually become resistant to available drugs. New drugs and treatment combinations are urgently needed to overcome treatment resistance.	Thank you for your comment. No action required.
	RC Path	No comments.	Thank you for your comment. No action required.

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	Takeda UK Ltd	The topic and evaluation route are appropriate	Thank you for your comment. No action required.
	UK Myeloma Society	This is a relevant and timely appraisal. Whilst treatments for myeloma have clearly improved, patients will die as a result of this condition. There are limited treatment options for patients who have received at least 4 prior lines of therapy. There is, therefore, a clear unmet need to provide better treatments to induce a longer and more durable period of remission and limit, or prevent, myeloma associated complications.	Thank you for your comment. NICE has scheduled this topic into its work programme. No action required.
Wording	Menarini-Stemline	There are a variety of inaccuracies in the Draft Scope. Due to the volume, these have been added as comments in the Draft Scope document.	Thank you for your comment. The scope has been updated to reflect this.
	Myeloma UK	The wording of the scope reflects the issues of clinical and cost effectiveness.	Thank you for your comment. No action required.
	RC Path	No comments.	Thank you for your comment. No action required.
	Takeda UK Ltd	No comments.	Thank you for your comment. No action required.

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	UK Myeloma Society	The wording of this scope is correct, although the listed comparators are mostly incorrect (see comments below).	Thank you for your comment.
Timing issues	Menarini-Stemline	Despite several treatments approved for myeloma in recent years, there are still significant unmet needs in the treatment pathway that selinexor potentially addresses. Given that myeloma remains a severe incurable, relapsing and remitting cancer, there is still an urgent need for new treatments, especially those with new mechanisms of action.	Thank you for your comment. NICE has scheduled this topic into its work programme. No action required.
	Myeloma UK	No comment	Thank you for your comment. No action required.
	RC Path	There are other technologies being assessed for r/r myeloma including BiTE therapies which hold more promise. I don't see this as a priority	Thank you for your comment. No action required.
	Takeda UK Ltd	No comments.	Thank you for your comment. No action required.
	UK Myeloma Society	This is a timely appraisal for reasons listed above.	Thank you for your comment. No action required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Menarini-Stemline	The Background Information is not inaccurate as such, but it is markedly different to that presented in the SVd Draft Scope (ID3797), and since this is paired appraisal taking place on the same timeline, the disease background information should share the same contextual information. We have amalgamated the two background sections into one, which we submit as a separate document.	Thank you for your comment. The background information in ID6193 and ID3797 have been aligned.
	Myeloma UK	The following statement from background information is inaccurate "Between 2016 and 2018, 5,041 people were diagnosed with myeloma in England." The 5041 figure is the average per year calculated from the 2016- 2018 registration data, not the total figure diagnosed between 2016 and 2018. The most up to date figure for 5-year survival is 56%. (https://digital.nhs.uk/data-and-information/publications/statistical/cancer-survival-in-england/cancers-diagnosed-2015-to-2019-followed-up-to-2020) NICE Technology Appraisal Guidance 695 is missing from the list of approved myeloma treatments available to patients after at least one prior therapy.	Thank you for your comment. The background information has been updated and NICE technology appraisal guidance 695 has been added to the scope.
	RC Path	Lists bortezomib monotherapy as a 2nd line therapy option which it is as per previous NICE TA129. However, in practice, bortezomib is never used as a monotherapy. It is generally used with dexamethasone or cyclophosphamide and dexamethasone which make it more efficacious therapy. KRD (carfilzomib, lenalidomide, dexamethasone) is also available as a 2nd line option through CDF	Thank you for your comments. The scope has been updated to note that bortezomib monotherapy at 2nd line is rarely used in clinical practice. NICE technology appraisal guidance 695 (carfilzomib plus lenalidomide and dexamethasone for multiple myeloma after

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			1 previous therapy, which included bortezomib) has been added to the scope.
	Takeda UK Ltd	For people whose disease is relapsed or refractory after at least 1 prior treatment, please add the following: “NICE technology appraisal guidance 695 recommends carfilzomib plus lenalidomide and dexamethasone as a treatment option for adults who had only 1 previous therapy, which included bortezomib” For people who have had at least 3 prior treatments, please add the following: “NICE technology appraisal guidance 658 recommends isatuximab plus pomalidomide and dexamethasone for use within the Cancer Drugs Fund as a treatment option for adults who have had 3 previous treatments including both lenalidomide and a proteasome inhibitor”	Thank you for your comments. NICE technology appraisal guidance 695 and 658 have been added to the scope.
	UK Myeloma Society	Yes	Thank you for your comment. No action required.
Technology	Menarini-Stemline	The regimen is described accurately as Selinexor with dexamethasone. The description of the technology and the relevant trial is not accurate. Selinexor is a novel, oral, selective inhibitor of nuclear export (SINE) compound that blocks exportin 1 (XPO1). It represents a novel mode of action in the treatment of multiple myeloma, that is refractory to current therapeutic options.	Thank you for your comment. The scope has been updated to include the marketing authorisation to describe the indication.

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		The phase 2b STORM trial was conducted in 2 parts, of which only Part 2 is relevant for this indication. Part 2 included patients with penta-exposed MM, defined as patients who have MM previously treated with lenalidomide, pomalidomide, bortezomib, carfilzomib, and daratumumab (and an alkylating agent), and triple-class-refractory MM, defined as patients whose disease is refractory to prior treatment with at least 1 IMiD, at least 1 PI, and the anti-CD38 monoclonal antibody (mAb) daratumumab (and glucocorticoids). A pre-specified subgroup included participants whose MM was documented to be refractory to bortezomib, carfilzomib, lenalidomide, pomalidomide, and daratumumab (BCLPD) - penta-refractory. The MHRA MA is based on this subgroup.	
	Myeloma UK	Selinexor with dexamethasone is licensed by the MHRA for the treatment of myeloma patients who have received at least four prior therapies and whose disease is refractory to at least two proteasome inhibitors, two immunomodulatory agents and an anti-CD38 monoclonal antibody, and who have demonstrated disease progression on the last treatment.	Thank you for your comment. The scope has been updated to include the marketing authorisation to describe the indication.
	RC Path	Is it being considered for only for patients who've had 4 or more prior line of therapy?	Thank you for your comment. The population has been updated to reflect the marketing authorisation for people with relapsed or refractory multiple myeloma who have had 4 or more treatments and whose disease is refractory to at least 2

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			proteasome inhibitors, 2 immunomodulatory agents and an anti-CD38 monoclonal antibody (penta-refractory), and who have demonstrated disease progression on the last therapy.
	Takeda UK Ltd	Yes	Thank you for your comment. No action required.
	UK Myeloma Society	Yes	Thank you for your comment. No action required.
Population	Menarini-Stemline	The description of the population is not accurate. In line with the UK MHRA MA, selinexor is indicated in penta-refractory multiple myeloma: selinexor in combination with dexamethasone for the treatment of multiple myeloma in adult patients who have received at least four prior therapies and whose disease is refractory to at least two proteasome inhibitors, two immunomodulatory agents and an anti-CD38 monoclonal antibody, and who have demonstrated disease progression on the last therapy.	Thank you for your comment. The population has been updated to reflect the marketing authorisation for people with relapsed or refractory multiple myeloma who have had 4 or more treatments and whose disease is refractory to at least 2 proteasome inhibitors, 2

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			immunomodulatory agents and an anti-CD38 monoclonal antibody (penta-refractory), and who have demonstrated disease progression on the last therapy.
	Myeloma UK	Yes, we consider the population to be appropriately defined.	Thank you for your comment. The population has been updated to reflect the marketing authorisation for people with relapsed or refractory multiple myeloma who have had 4 or more treatments and whose disease is refractory to at least 2 proteasome inhibitors, 2 immunomodulatory agents and an anti-CD38 monoclonal antibody (penta-refractory), and who have demonstrated disease progression on the last therapy.

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	RC Path	See above (Is it being considered for only for patients who've had 4 or more prior line of therapy?)	Thank you for your comment. The population has been updated to reflect the marketing authorisation for people with relapsed or refractory multiple myeloma who have had 4 or more treatments and whose disease is refractory to at least 2 proteasome inhibitors, 2 immunomodulatory agents and an anti-CD38 monoclonal antibody (penta-refractory), and who have demonstrated disease progression on the last therapy.
	Takeda UK Ltd	Yes	Thank you for your comment.
	UK Myeloma Society	Yes	Thank you for your comment.
Comparators	Menarini-Stemline	The seven comparators listed in the draft scope are not all appropriate as comparators in penta-refractory MM. Daratumumab monotherapy, ixazomib citrate plus lenalidomide and dexamethasone, and lenalidomide plus	Thank you for your comments. Daratumumab

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		dexamethasone are not recommended by NICE in patients who have had four prior lines and therefore are not appropriate at 5L+. Pomalidomide in combination with low-dose dexamethasone and panobinostat in combination with bortezomib and dexamethasone do have NICE guidance in treating patients after four prior treatments, however these recommendations are not specific to penta-refractory patients. UK clinical expert opinion sought by the company suggests penta-refractory patients would either have already been treated with these regimens, or these regimens would be unsuitable in the context of penta-refractory disease, and are therefore inappropriate comparators. UK expert clinician input describes that since there are currently no specific RRMM treatments for penta-refractory disease with NICE guidance, patients in the UK currently often seek compassionate use access to active treatments, or clinical trials of pipeline agents, where they are suitable for active treatment. Where access is not possible via these alternative routes, patients often receive a form of best supportive care, which may or may not also include conventional chemotherapy which they most commonly would expect to be cyclophosphamide (with or without dexamethasone).	monotherapy, ixazomib plus lenalidomide and dexamethasone, and lenalidomide plus dexamethasone have been removed as comparators in the scope. The comparators included are: pomalidomide in combination with low-dose dexamethasone, panobinostat in combination with bortezomib and dexamethasone, belantamab mafodotin (subject to ongoing NICE appraisal), conventional chemotherapy regimens, and best supportive care.
	Myeloma UK	The population outlined in the draft scope is “People with relapsed or refractory multiple myeloma who have had four or more treatments.” Therefore, this treatment will be given to patients from 5th line. Daratumumab monotherapy is only approved for use at 4th line and cannot be considered a comparator for the population outlined in the scope.	Thank you for your comments. Daratumumab monotherapy, ixazomib plus lenalidomide and dexamethasone, and

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		Other than daratumumab monotherapy, we agree that the treatments listed are approved/available for use at 5th line. However, this list does not reflect the treatments patients receive in clinical practice. For example: The combination of panobinostat plus bortezomib and dexamethasone is not widely used in clinical practice and should not be used as a comparator in this NICE appraisal. The combinations of lenalidomide plus dexamethasone and ixazomib, lenalidomide and dexamethasone are not widely used at fifth line as most patients will be refractory to lenalidomide have received lenalidomide at previous lines of treatment. The combination of pomalidomide and dexamethasone will not be suitable for patients who have received isatuximab, pomalidomide and dexamethasone or pomalidomide and dexamethasone at fourth line. Clinical trials and named patient/compassionate use schemes might be an option for patients at fifth line.	lenalidomide plus dexamethasone have been removed as comparators in the scope. The comparators included are: pomalidomide in combination with low-dose dexamethasone, panobinostat in combination with bortezomib and dexamethasone, belantamab mafodotin (subject to ongoing NICE appraisal), conventional chemotherapy regimens, and best supportive care.
	RC Path	1. Daratumumab is only funded for 4th line therapy and is therefore not a direct comparator for this which is beyond 4th line 2. Ixa/len/dex is funded for 3rd or 4th line therapy so is not a comparator	Thank you for your comments. The comparators in the scope have been updated and exclude daratumumab and ixazomib, lenalidomide and dexamethasone.

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	Takeda UK Ltd	In general yes. Please remove the following comparators, as these are not recommended by NICE guidance for patients who have had 4 prior treatments: • Daratumumab monotherapy – this is limited to patients who have had 3 prior treatments only • Ixazomib citrate plus lenalidomide and dexamethasone – this is limited to patients who have had 2 or 3 prior treatments only	Thank you for your comments. The comparators in the scope have been updated and exclude daratumumab and ixazomib, lenalidomide and dexamethasone.
	UK Myeloma Society	This scope includes many inappropriate comparators. The population is listed as those with relapsed or refractory multiple myeloma who have had 4 or more treatments. Selinexor with dexamethasone has been studied in the STORM trial in patients with relapsed or refractory multiple myeloma who: • Have had 3 or more lines including alkylating agent, lenalidomide, pomalidomide, bortezomib, pomalidomide, carfilzomib, daratumab and a glucocorticoid, and • Refractory to previous treatment with one or more glucorticoid, a proteosome inhibitor (bortezomib and or carfilzomib), and immunomodulatory agent (lenalidomide or pomalidomide) and an anti-CD38 monoclonal antibody (daratumumab). • There is a pre-specified 'penta-refractory' group of patients. In order to be compliant with the above statements within the current NHS-E pathway (ie treated at 5th line and beyond), patients receive: • Daratumumab at 1st (DVTD) or 2nd (DVD) or 4th (Dara mono) line. Daratumumab monotherapy is therefore not an appropriate comparator.	Thank you for your comments. Daratumumab monotherapy, ixazomib plus lenalidomide and dexamethasone, and lenalidomide plus dexamethasone have been removed as comparators in the scope. The comparators included are: pomalidomide in combination with low-dose dexamethasone, panobinostat in combination with bortezomib and dexamethasone, belantamab mafodotin

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		• Ixazomib Lenalidomide Dexamethasone at 3rd line (or 2nd line in the COVID pandemic). Ixazomib Lenalidomide Dexamethasone is therefore not an appropriate comparator. • Lenalidomide Dexamethasone at 1st/2nd or 3rd line. Rarely if ever beyond this. Lenalidomide Dexamethasone is therefore not an appropriate comparator. • Pomalidomide with Dexamethasone at 4th line in the majority of cases. Currently often given with Isatuximab via the Cancer Drug Fund. Pomalidomide is unlikely to be an appropriate comparator at 5th line. • Bortezomib in combination with Panobinostat is only given when they are sensitive to retreatment with Bortezomib. To receive Seliexor patients need to be refractory to a proteosome inhibitor. Bortezomib in combination with Panobinostat is not an appropriate comparator. Conventional chemotherapy and best supportive care are appropriate comparators.	(subject to ongoing NICE appraisal), conventional chemotherapy regimens, and best supportive care.
Outcomes	Menarini-Stemline	The outcomes listed in the draft scope are appropriate to capture the benefits.	Thank you for your comment. No action required.
	Myeloma UK	Yes	Thank you for your comment. No action required.
	RC Path	Is there a weighting to these outcome measures? Overall survival and quality of life should carry more weight	Thank you for your comment. No action required.

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	Takeda UK Ltd	Yes	Thank you for your comment. No action required.
	UK Myeloma Society	Yes	Thank you for your comment. No action required.
Economic analysis	Menarini-Stemline	Costs are considered from an NHS and Personal Social Services perspective. The cost effectiveness of the treatments is expressed in terms of incremental cost per quality-adjusted life year, as per the reference case. The cost-effectiveness model uses a partitioned survival analysis approach, whereby extrapolated OS, PFS and ToT outcomes are used to estimate the distribution of patients across health states over time. The health states in the model are progression-free, progressed disease and death, with the progression-free and progressed disease health states subdivided into on and off treatment. A lifetime time horizon of 30 years is considered, with modelled overall survival of approximately 0.1% after 30 years. This is in keeping with the reference case, which states that the time horizon should be sufficiently long to reflect any differences in costs or outcomes between the treatments.	Thank you for your comment. No action required.
	Myeloma UK	No comments.	Thank you for your comment. No action required.
	Takeda UK Ltd	No comments.	Thank you for your comment. No action required.

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	UK Myeloma Society	Yes.	Thank you for your comment. No action required.
Equality	Menarini-Stemline	Multiple myeloma (MM) is more common in: - Men than in women - Older people (43% of new cases of MM in England are in people aged ≥75 years [Cancer Research UK]) - People of African and Caribbean family background. No potential equality issues have been raised by stakeholders.	Thank you for your comment. No action required.
	Myeloma UK	No comments.	Thank you for your comment. No action required.
	Takeda UK Ltd	No comments.	Thank you for your comment. No action required.
	UK Myeloma Society	None known.	Thank you for your comment. No action required.
Other considerations	Menarini-Stemline	Recognising the complexity of the current myeloma treatment pathway, the company are taking a pragmatic approach and is working with the myeloma community, NHSE and NICE to ensure that the positioning of selinexor in each indication is clinically relevant and in the best interests of all stakeholders. Additionally, as both selinexor indications are being assessed	Thank you for your comment. No action required.

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		side by side, there will be the need for careful project management, coordination and communication with stakeholders to ensure the smooth, synergistic running of each appraisal.	
	Takeda UK Ltd	No comments.	Thank you for your comment. No action required.
	UK Myeloma Society	There is clearly an unmet clinical need for patients beyond 4 lines of treatment. The advantage of this technology is the fact it is an oral based therapy with a unique mechanism of action. It has a manageable side effect profile.	Thank you for your comment. No action required.
Innovation	Menarini-Stemline	Selinexor, a selective inhibitor of nuclear export compound that blocks exportin 1 (XPO1) and forces nuclear accumulation and activation of tumor suppressor proteins, inhibits nuclear factor κB, and reduces oncoprotein messenger RNA translation, is a potential novel treatment for myeloma that is refractory to current therapeutic options. In the context of this novel mode of action, selinexor represents an innovative approach to MM treatment, where the benefits of different modes of action are recognised throughout the patient treatment pathway.	Thank you for your comments. Innovation will be considered by the appraisal committee when formulating its recommendations. The company will have an opportunity to provide evidence on the innovative nature of its product in its submission. No action required.
	Myeloma UK	Selinexor is a new class of myeloma drug. It works in a different way from the myeloma drugs routinely commissioned for use in the UK. As a selective inhibitor of nuclear export, approval would introduce a novel treatment	Comments noted. The appraisal committee will discuss the potentially

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		approach into the pathway. This treatment is an all-oral combination. Whilst efficacy is the most important treatment benefit, patients also value treatments which are convenient, easy to take and limit hospital visits. Therefore, oral administration is substantial patient benefit which may not be captured in the QALY calculation.	innovative nature of this technology. No action required.
	Takeda UK Ltd	No comments.	Thank you for your comment. No action required.
	UK Myeloma Society	The technology has a unique mode of action targeting Exportin-1 (XPO1) that has been found overexpressed in multiple myeloma.	Comments noted. The appraisal committee will discuss the potentially innovative nature of this technology. No action required.
Questions for consultation	Menarini-Stemline	None at this time.	Thank you for your comment. No action required.
	Takeda UK Ltd	**Where do you consider selinexor with dexamethasone will fit into the existing care pathway for relapsed or refractory multiple myeloma?** As within the appraisal and the marketing authorisation submitted to the regulator, for patients who have had 4 or more treatments. **Would selinexor with dexamethasone be a candidate for managed access?** No comments.	Comments noted. The scope has been kept broad to ensure that NICE can appraise the technology within its marketing authorisation. No action required.

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		Do you consider that the use of selinexor can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation? No. **Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits**. No comment. **Questions re potential equality issues:** No equality issues identified. **NICE intends to evaluate this technology through its Single Technology Appraisal process:** This seems appropriate to us.	
	UK Myeloma Society	No.	Thank you for your comment. No action required.
Additional comments on the draft scope	Menarini-Stemline	As already flagged to NICE, there were serval inaccuracies and inconsistencies between the two appraisal scopes, so we have endeavoured to address these in our responses which we hope is helpful to NICE.	Thank you for your comment. Please see the updated background section. No action required.

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	Takeda UK Ltd	None.	Thank you for your comment. No action required.
	UK Myeloma Society	No.	Thank you for your comment. No action required.

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

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