National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Lenalidomide in combination with dexamethasone for previously untreated multiple myeloma

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

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Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Appropriateness	Celgene Ltd	No comments.	Thank you for your comments. The NICE team has taken into account the views of stakeholders, and it was decided that this technology should be evaluated through a technology appraisal.
	Janssen-Cilag Ltd	Yes, it is appropriate for this topic to be referred.	Thank you for your comments. The NICE team has taken into account the views of stakeholders, and it was decided that this technology should be

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			evaluated through a technology appraisal.
	UK Myeloma Forum	There is a need for an effective, well tolerated, all oral combination therapy for the treatment of newly diagnosed myeloma patients who are not eligible for transplant. Well over 60% of newly diagnosed patients are ineligible for SCT, and they often have significant comorbidities. The topic of this appraisal fulfils all of these criteria and is appropriate	Thank you for your comments. The NICE team has taken into account the views of stakeholders, and it was decided that this technology should be evaluated through a technology appraisal.
Wording	Celgene Ltd	No comments.	Comment noted. The wording of the remit/appraisal objective has been updated to include the full treatment regimen (that is, lenalidomide in combination with dexamethasone).
	Janssen-Cilag Ltd	The draft scope suggests the appraisal of “Lenalidomide” as a single agent. This is inconsistent with the marketing authorisation which states: “Lenalidomide in combination with dexamethasone until disease progression in patients who are not eligible for transplant” and	Comment noted. The wording of the remit/appraisal objective has been updated to include the full treatment regimen (that is, lenalidomide in

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		"Lenalidomide in combination with melphalan and prednisone followed by lenalidomide maintenance in patients who are not eligible for transplant". We propose that the licensed indication and regimen be made clear throughout the document.	combination with dexamethasone).
	UK Myeloma Forum	yes	Comment noted. The wording of the remit/appraisal objective has been updated to include the full treatment regimen (that is, lenalidomide in combination with dexamethasone).
Timing Issues	Celgene Ltd	No comments.	Comment noted. No action required.
	Janssen-Cilag Ltd	No comment	Comment noted. No action required.
	UK Myeloma Forum	Myeloma is not curable with current treatments and there is an urgent need to introduce therapies that not only lengthen progression free survival and overall survival but are also able to maintain quality of life both during and after therapy	Comment noted. No action required.

Comment 2: the draft scope

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Background information	Celgene Ltd	No comments.	Comment noted. No action required.
	Janssen-Cilag Ltd	The information is appropriate.	Comment noted. No action required.
	UK Myeloma Forum	The background is broadly accurate. In particular due to its incurable nature the main goals of therapy are to improve myeloma related symptoms by effectively controlling the disease for as long as possible with each therapy, improving overall survival and importantly maintaining quality of life. We would estimate that approximately 30 - 35% of newly diagnosed myeloma patients who require treatment will be transplant eligible. This appraisal is therefore applicable to approx. 65 - 70% of newly diagnosed myeloma patients. Current treatment approaches are guided by TA228 but also NHSE recommendations for baseline commissioning which support bortezomib usage. There is an approximate even split between patients who are treated with thalidomide / alkylator / steroid and bortezomib / alkylator / steroid. In terms of specific therapeutic combinations: CTD (cyclophosphamide / thalidomide / dexamethasone) is more commonly used than MPT (melphalan / thalidomide / dex) for those that receive thalidomide based therapy. VMP (bortezomib / melphalan / prednisolone) is the main bortezomib based combination treatment but some centres choose to use VCD (bortezomib / cyclophosphamide / dexamethasone) chemotherapy. It should be noted that there is postcode variable access to VMP via baseline commissioning following NHSE communications to several areas restricting access.	Comment noted. No action required. Comments noted. The availability of current treatments will be considered by the appraisal committee.

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The technology/ intervention	Celgene Ltd	The marketing authorisation for lenalidomide in the UK for treating 'adult patients with previously untreated multiple myeloma who are not eligible for transplant' is in combination with dexamethasone. Specifically, the second paragraph in this section should read, "Revlimid as combination therapy is indicated for the treatment of adult patients with previously untreated multiple myeloma who are not eligible for transplant." Celgene will be making a submission for lenalidomide in combination with dexamethasone (Rd) until disease progression. As such, "Lenalidomide" should be replaced by "Lenalidomide in combination with dexamethasone until disease progression" in the table.	The technology section has been updated so that it is consistent with the marketing authorisation wording in the Summary of Product Characteristics. The Intervention has been updated to 'Lenalidomide in combination with dexamethasone'.
	Janssen-Cilag Ltd	Unclear, we propose that the licensed indication and regimen be made clear throughout the document i.e., lenalidomide in combination with dexamethasone lenalidomide in combination with melphalan and prednisone.	The technology and intervention sections have been updated so that the wording is consistent with the marketing authorisation in the Summary of Product Characteristics.
	UK Myeloma Forum	Yes	Comment noted. No action required.

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Population	Celgene Ltd	No comments.	Comment noted. No action required.
	Janssen-Cilag Ltd	The population is defined appropriately.	Comment noted. No action required.
	UK Myeloma Forum	Yes. A specific subgroup that needs consideration is those patients for whom thalidomide based therapy is not appropriate due to contraindication / intolerance e.g. pre-existing peripheral neuropathy. Another subgroup requiring consideration are those who have had previous thrombosis or high thrombosis risk; the risk of thrombosis with thalidomide based treatments is recognised as being greater than either bortezomib based or lenalidomide based treatments.	Comment noted. The summary of the product characteristics outlines several special warnings and precautions for use. The risk of adverse effects of treatments may be taken into account in the cost-effectiveness modelling by the appraisal committee.
Comparators	Celgene Ltd	NICE TA228 guidance restricts bortezomib in combination with an alkylating agent and a corticosteroid specifically for patients who are unable to tolerate or have contraindications to thalidomide. Therefore, the following should be added to the scope to reflect this: “For people who are unable to tolerate, or have contraindications to thalidomide:	Comment noted. The comparators section has been updated.

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		• Bortezomib in combination with an alkylating agent and a corticosteroid." In addition, clinical experts stated that "best supportive care" is not used in clinical practice and therefore should be removed.	
	Janssen-Cilag Ltd	The comparators listed are appropriately consistent with existing NICE HTA appraisals and recommendations.	Comment noted. No action required
	UK Myeloma Forum	Best supportive care is not an option for active treatment and is not an appropriate comparator. The specific combination treatments that are established clinical practice in the UK are highlighted above i.e. Thalidomide based comparators are CTD and MPT whereas the bortezomib based comparator is VMP. There are no other relevant comparators	Comment noted. The comparators section has been updated.
Outcomes	Celgene Ltd	There are two additional outcome measures which are clinically relevant and should be included. These are: • Time to 2nd anti-myeloma therapy • Time to treatment failure.	Comment noted. The outcomes section has been updated.
	Janssen-Cilag Ltd	Yes	Comment noted. No action required.
	UK Myeloma Forum	Outcome measures are appropriate	Comment noted. No action required.

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Economic analysis	Celgene Ltd	A lifetime time horizon is appropriate to model multiple myeloma treatment and is consistent with the NICE reference case.	Comment noted. No action required.
	Janssen-Cilag Ltd	No comment	Noted. No action required.
	UK Myeloma Forum	Economic analysis is appropriate	Comment noted. No action required.
Equality and Diversity	Celgene Ltd	No comments.	Comment noted. No action required.
	Janssen-Cilag Ltd	No comment	Comment noted. No action required.
	UK Myeloma Forum	Patients who have myeloma and are transplant ineligible, range in their fitness from frail to relatively fit. There is a potential for inequality of access to treatment that requires regular attendance at their specialist treatment unit e.g. for injectable treatment for those who are less mobile or live a long distance from their treatment centre meaning they are less likely to attend / receive these treatments.	The benefits of different mode of administration will be taken into account in the appraisal.
Other considerations	Celgene Ltd	Clinical experts have informed Celgene that they do not wish to use Rd in the following subgroup in practice hence this is not appropriate and should be removed; • people who are unable to tolerate, or have contraindications to bortezomib and thalidomide	Comment noted. The subgroups have been amending in the scope.

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		To reflect NICE TA228, the following subgroup should be included in the comparators section of the scope of this appraisal: "For people who are unable to tolerate, or have contraindications to thalidomide: • Bortezomib in combination with an alkylating agent and a corticosteroid."	
	Janssen-Cilag Ltd	No comment	Comment noted. No action required.
Innovation	Celgene Ltd	In TA228, the committee stated that "The main objective of first-line therapy is to achieve a period of stable disease (termed the plateau phase) for as long as possible, thereby prolonging survival and maximising quality of life"1. This maybe especially important for elderly patients, in whom a response to rescue therapy at the time of first relapse may be difficult to achieve2. Rd is a step-change in the treatment of transplant ineligible NDMM. Its continuous use in the front line setting significantly improves PFS, reduces the risk of death, improves health-related quality of life and leads to lower rates of haematological adverse events compared with MPT, a standard of care given for a fixed treatment duration. Rd represents a clinically significant advantage, for older patients, in whom a response to rescue therapy may be difficult to achieve3. Rd is also an all oral combination and patients have shown a preference for oral combinations in numerous studies4. As an oral therapy Rd can be self-administered at home, with only outpatient consultations during the course of	Comment noted. No action required.

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		treatment. This is different to bortezomib which is administered subcutaneously or intravenously in a hospital setting. This can be of immense help to patients who have mobility problems and also allows patients to live a more normal life without disruptions.	
	Janssen-Cilag Ltd	No comment	Noted. No action required.
	UK Myeloma Forum	Continuous application of antimyeloma therapy is a paradigm shift in treatment approach for this incurable cancer. The ability to deliver a tolerable treatment, which is effective to control myeloma for substantial periods, has been achieved with Lenalidomide. Lenalidomide / dexamethasone is a highly effective and well tolerated all oral treatment which is likely to be popular with patients and be associated with improvements in quality of life due to its manageable side effect profile and lack of requirement for weekly attendance at treatment unit. The data for the appraisal is based on well conducted phase 3 trials (with appropriate comparators for the time period in which the trial was carried out). The main data sources are: CTD (1 phase 3 trial CTD v MP, Morgan et al Blood 2011; Limited PFS benefit, no OS benefit) MPT : 6 randomised trials comparing MPT v MP – meta-analysis Fayers et al. Blood 2011 (PFS and OS benefit) VMP – 1 phase 3 trial VMP v MP – San Miguel NEJM 2008; Mateos J Clin Onc 2011 (PFS and OS benefit) Rd – Benboubker NEJM 2014 (PFS and OS benefit)	Comment noted. No action required.

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Questions for consultation	Celgene Ltd	**Question:** Which treatments are considered to be established clinical practice in the NHS: • for previously untreated multiple myeloma in people for whom stem-cell transplantation is considered inappropriate? **Answer:** All treatments which are considered to be established clinical practice in the NHS are covered in the above sections. • for people who are unable to tolerate, or have contraindications to bortezomib and thalidomide? **Answer:** Clinical experts have informed Celgene that they do not wish to use Rd in the following subgroup in practice hence this is not appropriate and should be removed from the 'Other considerations' section of the scope. **Question:** Have all relevant comparators for lenalidomide been included in the scope? **Answer:** Yes **Question:** Are the subgroups listed above appropriate for people in whom lenalidomide is expected to be more clinically effective and cost effective or other groups?	Comments noted. Please see responses to comments on other sections of the scope.

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		Answer: Clinical experts have informed Celgene that they do not wish to use Rd in the following subgroup in practice hence this is not appropriate and should be removed from the 'Other considerations' section of the scope; • people who are unable to tolerate, or have contraindications to bortezomib and thalidomide In line with TA228 guidance, the subgroup of interest is: • people who are unable to tolerate, or have contraindications to thalidomide **Question:** Are there any other subgroups which should be included? **Answer:** To reflect NICE TA228, the following subgroup should be included in the comparators section of the scope of this appraisal: "For people who are unable to tolerate, or have contraindications to thalidomide: • Bortezomib in combination with an alkylating agent and a corticosteroid." **Question:** Where do you consider lenalidomide will fit into the existing NICE pathway, 'Blood and bone marrow cancers'? **Answer:** Under 'Transplant-ineligible patients: first line treatment' alongside bortezomib and thalidomide.	

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		Question: NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope: • could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which lenalidomide will be licensed; • could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts. **Answer:** No equity or equality issues have been identified. **Question:** Do you consider lenalidomide to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)? **Answer:** Yes, please see above under innovation.	

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		Question: Do you consider that the use of lenalidomide can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation? Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits. **Answer:** Yes, described above under innovation. The benefits come from the fact that Rd is an all oral combination which can be taken at home.	
	Janssen-Cilag Ltd	No comment	Noted. No action required.
	UK Myeloma Forum	Additional questions not answered above: Treatment for people for whom thalidomide / bortezomib is not appropriate: These patients have individualised pathway based on general performance status/ comorbidities/ and their relative tolerance to other treatments. Historical combination chemotherapy treatments such as melphalan / prednislone or cyclophosphamide / dexamethasone would be considered – although are recognised as being significantly less efficacious. It is likely that in practice short courses of steroids steroid +/- mel or cyclo would be used and rapidly assessed as having failed to enable rapid movement of the patient to 3rd line therapy to received lenalidomide dexamethasone (TA171). In terms of the NICE pathway it is envisaged that lenalidomide would fit at 1st line as well as at relapse for those who are lenalidomide naïve.	Comment noted. The subgroup for people for whom thalidomide / bortezomib is not appropriate has been removed.