National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Elotuzumab for previously treated multiple myeloma [ID855]

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

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	Bristol-Myers Squibb	Yes. Elotuzumab for previously treated multiple myeloma (MM) is an appropriate topic for appraisal.	Comments noted. No action required.
	Celgene	No comments	Comments noted. No action required.
	Myeloma UK	Myeloma UK considers this to be an important topic to refer to NICE for appraisal.	Comments noted. No action required.
	Royal College of Pathologists and British Society of Haematology	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	Comments noted. No action required.

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	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.	Comments noted. No action required.
Wording	Bristol-Myers Squibb	Yes. We agree that it is important to appraise the clinical and cost effectiveness of elotuzumab within its marketing authorisation for previously treated multiple myeloma	Comments noted. No action required.
	Celgene	No comments	Comments noted. No action required.
	Myeloma UK	At present, given that marketing authorisation has not yet been granted, we consider the wording of the remit to be accurate.	Comments noted. No action required.
	Royal College of Pathologists and British Society of Haematology	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	Comments noted. 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.	Comments noted. No action required.
Timing Issues	Bristol-Myers	It is important for NICE to provide a recommendation for the use of	Comments noted. NICE can only begin to

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	Squibb	elotuzumab within the NHS as close as possible to marketing authorisation.	appraise a technology when it has been formally referred by the Secretary of State for Health. NICE aims to provide draft guidance to the NHS within 6 months from the date when the marketing authorisation for a technology is granted.
	Celgene	No comments	Comments noted. No action required.
	Myeloma UK	The NICE scoping of elotuzumab is timely. As mentioned above, given that the marketing authorisation has not yet been granted by the European Medicines Agency (EMA), this may have a bearing on the timings of the appraisal.	Comments noted. NICE can only begin to appraise a technology when it has been formally referred by the Secretary of State for Health. NICE aims to provide draft guidance to the NHS within 6 months from the date when the marketing authorisation for a

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			technology is granted.
	Royal College of Pathologists and British Society of Haematology	Almost all patients with myeloma will experience disease relapse with eventual development of drug restance and eventual death. There is an urgent need for new therapies for myeloma for use either as monotherapy or in combination which are able to induce longer remissions and extend survival while maintaining quality of life.	Comments noted. 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.	Comments noted. No action required.
Additional comments on the draft remit	Bristol-Myers Squibb	No further comments	Comments noted. No action required.
	Celgene	No comments	Comments noted. No action required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Celgene	Elotuzumab has also been studied in combination with lenalidomide and dexamethasone in patients with previously untreated multiple myeloma (ELO	Comments noted. No action required.

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		1 substudy: NCT01891643/ ELOQUENT -1: NCT01335399).	
	Myeloma UK	We consider the background information to be largely accurate. However, it broadly concentrates on the NICE approved drugs for myeloma patients in the relapsed setting. Whilst we understand that this is due to the setting of the appraisal (i.e. first relapse and beyond), the background information should consider previous treatments that patients have received (e.g. thalidomide, bortezomib) and whether they have had intensive (i.e. high-dose therapy and stem cell transplantation [HDT-SCT]) or non-intensive treatment (i.e. chemotherapy rather than HDT-SCT).	Comments noted. The background is only intended to provide a brief overview of the condition and current treatment options. A more detailed description of treatment options for people with multiple myeloma will be included in the company's submission. The proposed technology appraisal is for elotuzumab for previously treated myeloma. Attendees at the scoping workshop confirmed that after first-line treatment, all people with multiple myeloma would generally follow the same treatment

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			pathway.
	Royal College of Pathologists and British Society of Haematology	This is largely accurate. I also wish to point out 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. Newly diagnosed patients, whether they are transplant eligible or transplant ineligible are increasingly treated with bortezomib regimens at frontline, according to NICE TA311 and NICE TA228. Bortezomib received approval for routine commissioning by NHSE in June 2013. This means that a significant proportion of patients will have receive a bortezomib based treatment at first line, and for some, bortezomib as indicated by NICE as second line therapy may be inappropriate (due for example to a short remission period).	Comments noted. The background is only intended to provide a brief overview of the condition and current treatment options. A more detailed description of treatment options for people with multiple myeloma will be included in the company's submission.
	UK Myeloma Forum	This is largely accurate. It is also important to acknowledge the presence of NICE guidance for treatment of newly diagnosed patients as this will effect 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. NICE TA311 is applicable to patients for whom stem cell transplant is planned and approves the use of bortezomib / dexamethasone or bortezomib / thalidomide / dexamethasone. 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, following	Comments noted. The background is only intended to provide a brief overview of the condition and current treatment options. A more detailed description of treatment options for people with multiple myeloma will be included in the

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		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 second line therapy is inappropriate for a proprotion of patients.	company's submission.
The technology/ intervention	Celgene	Celgene understand that the elotuzumab combination with bortezomib and dexamethasone is still at phase II (NCT01478048). The timelines for completing the phase II and a phase III study will put this combination outside of this review.	Comments noted. Elotuzumab will be appraised within its marketing authorisation for treating multiple myeloma.
	Myeloma UK	The description of the technology is accurate.	Comments noted. No action required.
	Royal College of Pathologists and British Society of Haematology	Yes.	Comments noted. No action required.
	UK Myeloma Forum	Yes	Comments noted. No action required.
Population	Bristol-Myers Squibb	The population is defined appropriately.	Comments noted. No action required.

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	Celgene	This should specify adult patients.	Comment noted. Elotuzumab will be appraised within its marketing authorisation for treating multiple myeloma.
	Myeloma UK	Myeloma UK considers the population to be defined appropriately.	Comments noted. No action required.
	Royal College of Pathologists and British Society of Haematology	Published Phase 3 clinical trials included patients who had received 1 - 3 prior lines of therapy prior to receiving Elotuzumab based treatment. As such the population under consideration should be those who have received 1 - 3 lines of prior therapy.	Comments noted. Elotuzumab will be appraised within its marketing authorisation for treating multiple myeloma.
	UK Myeloma Forum	Published Phase 3 clinical trials included patients who had received 1 - 3 prior lines of therapy prior to receiving Elotuzumab based treatment. As such the population under consideration should be those who have received 1 - 3 lines of prior therapy.	Comments noted. Elotuzumab will be appraised within its marketing authorisation for treating multiple myeloma.
Comparators	Bristol-Myers Squibb	We understand the comparators listed in the draft scope are representative of the standard treatments used in the NHS.	Comments noted. The comparators have been

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		Please note that while the comparators discussed may represent treatments used in the NHS, it is currently unclear whether comparative evidence will be available to compare all of these treatments in the different settings discussed with elotuzumab.	updated. At the scoping workshop attendees agreed that bortezomib (with or without dexamethasone) and lenalidomide in combination with dexamethasone were the most relevant comparators for elotuzumab. NICE is developing guidance for panobinostat for treating multiple myeloma after 2 prior therapies and would be considered a relevant treatment option for this population (subject to the ongoing NICE guidance). Attendees further explained that people with multiple myeloma after 3 prior therapies are likely to be refractory to both bortezomib and lenalidomide (because of prior exposure to

Section	Consultee/ Commentator	Comments [sic]	Action
			both drugs) and therefore it is very unlikely that elotuzumab would be used at fourth-line and beyond in clinical practice.
	Celgene	No comments.	Comments noted. No action required.
	Myeloma UK	We have the following comments on the comparators: After 1 therapy - Bortezomib is almost never used as a monotherapy. Bortezomib in combination with dexamethasone is therefore the most appropriate comparator in this setting and corresponds to comparators in elotuzumab clinical trials. - Lenalidomide in combination with dexamethasone is an appropriate comparator in this appraisal. However, it should be noted that if NICE approve lenalidomide in this setting, it will narrow the numbers of myeloma patients accessing the treatment on the NHS (i.e. it is approved by the Cancer Drugs Fund (CDF) for all patients in this setting, whereas NICE would limit it to patients who received Velcade as a result of TA228). It should also be noted that the CDF is currently undergoing another review, which could mean that this setting of lenalidomide may (or may not) be removed from the	Comments noted. The comparators have been updated. At the scoping workshop attendees agreed that bortezomib (with or without dexamethasone) and lenalidomide in combination with dexamethasone were the most relevant comparators for elotuzumab. NICE is developing guidance for panobinostat for

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		nationally approved list of drugs. After 2 or more therapies - It should be noted that as bortezomib retreatment has been removed from the CDF approved list, patients will only receive bortezomib in clincially exceptional circumstances. It therefore isn't the most appropriate comparator in this setting. - Lenalidomide and dexamethasone is the most appropriate comparator in this setting, given the comparator in the ELOQUENT-2 trial and the fact that all myeloma patients can access it on the NHS. - Patients in Wales do not routinely receive pomalidomide and bendamustine in this setting, although an AWMSG decision is pending. - Whilst pomalidomide is available to patients in England via the CDF, the CDF nationally approved list of drugs is set to be reviewed which could mean that pomalidomide may be removed. - Thalidomide is sometimes used in this setting, in combination with chemotherapy. - It should be noted that in the multiply relapsed setting given the lack of routinely available treatments and individual disease history - there is not a standard of care in this setting. - As identified in previous NICE appraisals in the multiply relapsed setting, there is limited comparative data in this setting (for example, whilst bendamustine is an effective treatment there is very little clinical trial	treating multiple myeloma after 2 prior therapies and would be considered a relevant treatment option for this population (subject to the ongoing NICE guidance). Attendees further agreed that pomalidomide in combination with low-dose dexamethasone, bendamustine and conventional chemotherapy regimens were not relevant comparators for elotuzumab.

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		information available). This is something that should be discussed during the scoping meeting.	
	Royal College of Pathologists and British Society of Haematology	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 to due inferior efficacy. An increasingly large proportion of patients who have received bortezomib based treatment at first line will receive lenalidomide / dexamethasone as 2nd line therapy funded by the Cancer Drugs Fund. The comparators at 2nd line should include the above. At 3rd line Lenalidomide / dexamethasone as approved by NICE is the standard of care. A proportion of patients will have received this at 2nd line in which case Pomalidomide / dexamethasone is the commonest used 3rd line therapy which is funded by the Cancer Drugs Fund. However, please note that pomalidomide / dexamethasone is not an appropriate comparator for Elotuzumab / Lenalidomide / Dexamethasone as current access to pomalidomide mandates prior exposure and relapse / refractoriness to lenalidomide / dexamethasone. Such patients were excluded from the Phase 3 study. Beyond 3rd line therapy bendamustine based treatment is the commonest approach, funded by the Cancer Drugs Fund. The use of conventional chemotherapy including vincristine, doxorubicin are not commonly used in this setting. The use of melphalan and cyclophosphamide are used mainly as a palliative chemotherapy option.	Comments noted. The comparators have been updated. At the scoping workshop attendees agreed that bortezomib (with or without dexamethasone) and lenalidomide in combination with dexamethasone were the most relevant comparators for elotuzumab. NICE is developing guidance for panobinostat for treating multiple myeloma after 2 prior therapies and would be considered a relevant treatment option for this population (subject to the ongoing NICE

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			guidance). Attendees further agreed that pomalidomide in combination with low-dose dexamethasone, bendamustine and conventional chemotherapy regimens were not relevant comparators for elotuzumab.
	UK Myeloma Forum	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. An increasingly large proportion of patients who have received bortezomib based treatment at first line will receive lenalidomide / dexamethasone as 2nd line therapy funded by the Cancer Drugs Fund. The comparators at 2nd line should include the above. At 3rd line Lenalidomide / dexamethasone as approved by NICE is the standard of care. A proportion of patients will have received this at 2nd line in which case Pomalidomide / dexamethasone is the commonest used 3rd line therapy which is funded by the Cancer Drugs Fund. However, please note that pomalidomide / dexamethasone is not an appropriate comparator for Elotuzumab / Lenalidomide / Dexamethasone as current access to pomalidomide mandates prior exposure and relapse / refractoriness to	Comments noted. The comparators have been updated. At the scoping workshop attendees agreed that bortezomib (with or without dexamethasone) and lenalidomide in combination with dexamethasone were the most relevant comparators for elotuzumab. NICE is

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		lenalidomide / dexamethasone. Beyond 3rd line therapy bendamustine based treatment is the commonest approach, funded by the Cancer Drugs Fund. The use of conventional chemotherapy including vincristine, doxorubicin are not commonly used in this setting. The use of melphalan and cyclophosphamide are used mainly as a palliative chemotherapy option.	developing guidance for panobinostat for treating multiple myeloma after 2 prior therapies and would be considered a relevant treatment option for this population (subject to the ongoing NICE guidance). Attendees further agreed that pomalidomide in combination with low-dose dexamethasone, bendamustine and conventional chemotherapy regimens were not relevant comparators for elotuzumab.
Outcomes	Bristol-Myers Squibb	The outcomes included in the draft scope are appropriate.	Comments noted. No action required.
	Celgene	PFS2 should be included if it has been measured in the trials.	Comments noted. No

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			changes to the scope required. During the scoping workshop, attendees agreed that the most appropriate outcomes for elotuzumab had been listed in the draft scope.
	Myeloma UK	We consider these outcome measures to be appropriate.	Comments noted. No action required.
	Royal College of Pathologists and British Society of Haematology	Yes. Progression free survival as a surrogate for overall survival is an important outcome measure	Comments noted. No action required.
	UK Myeloma Forum	Yes. Progression free survival as a surrogate for overall survival is an important outcome measure	Comments noted. No action required.
Economic analysis	Bristol-Myers Squibb	Some manufacturers have negotiated confidential price discounts to make their drugs available on the CDF. In order to compare against treatments funded by the CDF, the costs incurred by the CDF will need to be provided. If this is not possible, we will be required to use the list price in the base case and explore different price scenarios as a sensitivity analysis.	Comments noted. Once the technology receives a formal referral by the Secretary of State for Health, NICE offers the company an opportunity to discuss its evidence

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			submission at a post referral decision problem meeting.
	Celgene	Inclusion of comparators at CDF prices is unlikely to be feasible as individual companies have confidentiality agreements with NHS England over the pricing and this doesn't include disclosure to other bodies such as NICE.	Comments noted. Once the technology receives a formal referral by the Secretary of State for Health, NICE offers the company an opportunity to discuss its evidence submission at a post referral decision problem meeting.
	Myeloma UK	NA	Comments noted. No action required.
	Royal College of Pathologists and British Society of Haematology	Agree regarding appropriately long time horizon	Comments noted. No action required.
	UK Myeloma Forum	Agree regarding appropriately long time horizon	Comments noted. No action required.
Equality and	Bristol-Myers	No equality issues have been identified.	Comments noted. No

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Diversity	Squibb		action required.
	Celgene	No comments	Comments noted. No action required.
	Myeloma UK	NA	Comments noted. No action required.
	Royal College of Pathologists and British Society of Haematology	There are no equality issues for this therapy	Comments noted. No action required.
	UK Myeloma Forum	There are no equality issues for this therapy	Comments noted. No action required.
Innovation	Bristol-Myers Squibb	Despite the improvement in response rates and survival from front line treatment options, MM remains an incurable disease and nearly all patients with MM relapse. The need for additional treatment options for this disease remains high and elotuzumab has a different mode of action to agents currently used in clinical practice. Innovative New Approach in MM – Immunostimulatory Antibody Elotuzumab (BMS-901608, HuLuc63) is a novel humanized IgG1 monoclonal antibody (mAb) targeted against signalling lymphocyte activation molecule family 7 (SLAMF7), a glycoprotein expressed on myeloma and natural killer (NK) cells. It is an immunostimulatory antibody that is unique from other	Comments noted. The potential innovative nature of the technology will be considered by the Appraisal Committee.

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		therapeutic mAbs. Elotuzumab exerts a dual effect by mediating antibody-dependent cellular cytotoxicity (ADCC) and directly stimulating NK cells. The target of elotuzumab (SLAMF7) has restricted expression which limits off-target effects and affords a favourable safety profile. Combinations of elotuzumab with lenalidomide and bortezomib demonstrated preclinical synergy in MM. Data from clinical trials have demonstrated elotuzumab is the first immunostimulatory monoclonal antibody demonstrating a significant and clinically meaningful increase in progression-free survival (PFS) and overall response rate (ORR) in a large, randomized phase 3 trial in patients with relapsed or refractory multiple myeloma (RRMM). In this trial minimal incremental adverse events were seen with the addition of elotuzumab to lenalidomide and dexamethasone. Elotuzumab has the potential to represent a 'step change' in terms of mechanism of action and potential clinical efficacy, in an area of unmet clinical need.	
	Celgene	No comments	Comments noted. No action required.
	Myeloma UK	Elotuzumab is a first-in-class monoclonal antibody (immunotheraputic drug) and the evidence published to date suggests that it is very innovative in terms of its mechanisms of action. Immunotherapy is an extremely promising area of drug development in myeloma. An innovative attribute of elotuzumab is that it has two mechanisms of action	Comments noted. The potential innovative nature of the technology will be considered by the Appraisal Committee.

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		- it binds to the SLAMF7 (also known as CS-1) protein found on the surface of myeloma cells and attracts "natural killer" lymphocytes in the immune system. This enables the immune system to target and kill the myeloma cells. Clinical trials have shown that elotuzumab works well when used in combination with routinely available myeloma drugs, namely bortezomib and lenalidomide (in combination with dexamethasone). When elotuzumab is added to these drugs, progression free survival (PFS) is prolonged. ELOQUENT-2 study found that adding elotuzumab to lenalidomide and dexamethasone in relapsed patients, PFS is extended by 4.5 months and risk of myeloma progression was reduced by 30%. Other results of trials looking at elotuzumab in combination with bortezomib and dexamethasone, also highlight that it is an extremely effective combination treatment in relapsed and/or refractory myeloma.	
	Royal College of Pathologists and British Society of Haematology	Yes. This is a new class of drug with a new mechanism of action, that appears synergistic in combination with existing therapies and has firm Phase 3 evidence to support it. A unique feature of this technology is the ability to activate immune cells, by binding to the CS1 receptor present on those cells. The data available to aid the appraisal comprises published Phase 3 clinical trial results of the technology in combination with lenalidomide / dexamethasone in comparison to lenalidomide / dexamethasone alone	Comments noted. The potential innovative nature of the technology will be considered by the Appraisal Committee.
	UK Myeloma	Yes. This is a new class of drug which appears synergistic in combination	Comments noted. The potential innovative

Section	Consultee/ Commentator	Comments [sic]	Action
	Forum	with existing therapies and has firm Phase 3 evidence to support it. The data available to aid the appraisal comprises published Phase 3 clinical trial results of the technology in combination with lenalidomide / dexamethasone in comparison to lenalidomide / dexamethasone alone	nature of the technology will be considered by the Appraisal Committee.
Other considerations	Celgene	No comments	Comments noted. No action required.
	Myeloma UK	NA	Comments noted. No action required.
Questions for consultation	Celgene	No comments	Comments noted. No action required.
	Janssen-Cilag UK	As well as subgroup analyses by number of lines of previous therapy, the type of prior therapy (proteasome inhibitor vs immunomodulatory agent vs both) and whether or not patients are refractory to prior treatment(s) could inform important subgroups.	Comments noted. No changes to the scope required. During the scoping workshop, attendees agreed that these subgroups were not relevant for this proposed appraisal given all people generally follow the same treatment

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			pathway after first-line treatment, and because of the anticipated position in the treatment pathway for elotuzumab.
	Myeloma UK	We anticipate that elotuzumab will most likely be used in the relapse and/or refractory setting, either in combination with bortezomib and dexamethasone or in combination with lenalidomide and dexamethasone. NICE need to think carefully about the appraisal of elotuzumab and how it will fit in with other appraisals in the same setting. Currently, NICE have referred carfilzomib and panobinostat to the NICE appraisal committees which are likely to be in the same setting at elotuzumab. There are also lenalidomide and pomalidomide appraisals that are ongoing for relapsed patients. As the myeloma treatment pathway will become even more complex, NICE and the myeloma community need to establish how best to use the new treatments coming down the pipeline in the most clincially relevant ways. There is the potential for meetings to be held outside of appraisal process to discuss the myeloma treatment pathway to ensure it is clincially relevant.	Comments noted. At the scoping workshop, attendees agreed an STA was the most appropriate process to consider this topic.
	Royal College of Pathologists and British Society of Haematology	It is likely that the technology would fit into the current NICE pathway replacing the exisiting guidance for treatment of relapsed therapy with Lenalidomide and Dexamethasone (TA171)	Comments noted. No action required.

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	UK Myeloma Forum	It is likely that the technology would fit into the current NICE pathway replacing the exisiting guidance for treatment of relapsed therapy with Lenalidomide and Dexamethasone (TA171)	Comments noted. No action required.
Additional comments on the draft scope	Celgene	No additional comments	Comments noted. No action required.

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

- Department of Health
- Healthcare Improvement Scotland