National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Pomalidomide with dexamethasone for treating relapsed and refractory multiple myeloma after at least two regimens including lenalidomide and bortezomib (review of TA338)

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

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.

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Celgene	No comments	Comments noted. No action required.
	Myeloma UK	Myeloma UK considers the background information within the appraisal to be accurate. There are other ongoing NICE assessments taking place in the relapse setting, which might be useful to reference for context.	Comments noted. The 'Related NICE recommendations and NICE Pathways' section of the scope has been updated.
	UK Myeloma Forum	Background information describing multiple myeloma is broadly correct. The treatment landscape for myeloma is changing, and the scoping document needs to reflect how therapy at relapse is decided by response to and toxicity of prior treatments. Currently newly diagnosed patients will receive bortezomib or thalidomide as upfront therapy (TA 311 or TA 228), consolidated with high dose	Comments noted. The background is only intended to provide a brief overview of the condition and current treatment options. A more detailed

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		chemotherapy in suitable patients. At first relapse (2nd line) Bortezomib is NICE approved (TA129). This is applicable to patients who are bortezomib naïve or those who have previously received bortezomib and had suitable depth and duration of response without significant treatment related toxicity (such as neurotoxicity). A proportion of patients may have received lenalidomide at first relapse if they were unsuitable for bortezomib (available via the Cancer Drugs Fund until November 2015). At second relapse (3rd line) TA171 and TA380 are applicable (note commissioning via NHS England does not support TA380 until 26th April 2016 at the maximum 3 month implementation date from issue of TA380). Currently most patients at 3rd line receive Lenalidomide / Dexamethasone as per TA171. For those who have previously received lenalidomide (e.g. via CDF) an alternative available treatment is Bendamustine based treatment (via CDF). Bortezomib / Panobinostat / dexamethasone will be an alternative therapy at this point when it becomes available via commissioning for those patients who did not have significant toxicity with prior bortezomib. At 3rd relapse (4th line) treatment would depend on what previous treatments and response and toxicity to previous treatments. The only available active therapies at this point currently are bendamustine based (via CDF) and from 26/4/16 Bortezomib / panobinostat / dexamethasone (TA380 – caveats as above). The phrase “combination chemotherapy” is used in the scope, this would be more appropriately phrased “conventional chemotherapy” and is applied to drugs such as melphalan, cyclophosphamide. The use of these is based on historical evidence prior to the introduction of newer treatments such as	description will be included in the company’s submission.

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		thalidomide / bortezomib / lenalidomide. Whilst these may be used in some centres they would generally be considered as a more palliative approach rather than an active approach (in comparison to the treatments outline above). There is not evidence to support the use of these agents at this stage of therapy in the modern era of myeloma therapy.	
The technology/ intervention	Celgene	No comments	Comments noted. No action required.
	Myeloma UK	We consider the description of the technology to be accurate.	Comments noted. No action required.
	Napp Pharmaceuticals	Yes	Comments noted. No action required.
	UK Myeloma Forum	Yes.	Comments noted. No action required.
Population	Celgene	No comments	Comments noted. No action required.
	Myeloma UK	Yes. The population covered is in line with the marketing authorisation by the European Medicines Agency (EMA) and we consider this to be accurate.	Comments noted. No action required.
	Napp Pharmaceuticals	Yes	Comments noted. No action required.
	Novartis Oncology	Were patients whose prior treatment was IMID and dexamethasone combination or bortezomib and dexamethasone therapy included in the study?	Comments noted. Submissions are invited from the company. The company should identify

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			all evidence relevant to the appraisal, and clearly describe the populations enrolled into each of the studies.
	UK Myeloma Forum	The population is correctly defined according to the marketing authorisation for Pomalidomide in the UK.	Comments noted. No action required.
Comparators	Celgene	Panobinostat plus bortezomib plus dexamethasone (PBD) should be a comparator for after 2 or more prior therapies. The scope currently specifies only after 2 prior therapies. Combination chemotherapy regimens should not be a comparator. The clinical experts (Professor Kwee Yong and Dr Mathew Streetly) at the recent daratumumab scoping meeting (21/03/16) advised that they use bendamustine and not combination chemotherapies as the toxicity is generally unacceptably high and there is no real efficacy data at 4th and 5th line.	Comments noted. The 'Comparators' section of the scope has been updated. In NICE technology appraisal guidance 338, the committee heard from the clinical expert that conventional alkylating agents such as melphalan or cyclophosphamide were relevant comparators for pomalidomide, and highlighted that clinical practice varies. When selecting the most appropriate comparator(s), the

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			committee will consider: • established NHS practice in England • the natural history of the condition without suitable treatment • existing NICE guidance • cost effectiveness • the licensing status of the comparator. For more details, please see sections 6.2.1–6.2.4 of NICE's guide to the methods of technology appraisal (2013).
	Myeloma UK	The comparators are largely accurate. Please note that for multiply relapsed (i.e. beyond second/third relapse) myeloma patients in the setting covered by the appraisal there is not a routine standard of care for patients – it depends on clinical decision-making and the individual patient in question. Melphalan and prednisolone are just one example of a chemotherapy combination that patients might receive at this	Comments noted. When selecting the most appropriate comparator(s), the committee will consider: • established NHS

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		stage.	practice in England • the natural history of the condition without suitable treatment • existing NICE guidance • cost effectiveness • the licensing status of the comparator. For more details, please see sections 6.2.1–6.2.4 of NICE's guide to the methods of technology appraisal (2013).
	Napp Pharmaceuticals	Yes	Comments noted. No action required.
	Novartis Oncology	We recommend that panobinostat / bortezomib/ dexamethasone combination should be included as a comparator for Pomalidomide after 3 prior treatment	Comments noted. The 'Comparators' section of the scope has been updated.
	UK Myeloma Forum	The published phase 3 clinical trial for patients receiving pomalidomide had strict inclusion criteria (MM-003, San Miguel et al Lancet Oncology 2013).	Comments noted. In NICE technology

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		Patients needed to have received both lenalidomide and bortezomib, and be refractory (or at least intolerant) to both of these drugs A suitable comparator at 3rd line therapy would be Panobinostat with bortezomib and dexamethasone (TA380) for those who had previously received and were refractory bortezomib and lenalidomide. Beyond 3rd line Bendamustine based treatment (via CDF) would be the most appropriate comparator. Conventional chemotherapy such as melphalan and cyclophosphamide would not be a suitable comparator in preference to bendamustine. They are generally used as a last line therapy. High dose dexamethasone (as per the control arm of MM-003) would be a potential comparator but it is not routine used in the UK in this way (high dose dexamethasone may be considered an “active” treatment whereas as low dose dexamethasone (<160mg/28days for 1-2 months) would be generally consider a palliative approach)	appraisal guidance 338, the committee heard from the clinical expert that conventional alkylating agents such as melphalan or cyclophosphamide were relevant comparators for pomalidomide, and highlighted that clinical practice varies. The committee further heard from the clinical expert that because of its adverse effects, high-dose dexamethasone is now no longer an option for people whose disease has previously been treated with bortezomib and lenalidomide in clinical practice. When selecting the most appropriate comparator(s), the

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			committee will consider: • established NHS practice in England • the natural history of the condition without suitable treatment • existing NICE guidance • cost effectiveness • the licensing status of the comparator. For more details, please see sections 6.2.1–6.2.4 of NICE's guide to the methods of technology appraisal (2013).
Outcomes	Celgene	TTF will be used for the economic model and should be included as an outcome.	Comments noted. The outcomes specified in the scope are consistent with the outcomes specified across all NICE technology appraisals

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			of technologies for treating cancers. Other clinically relevant outcomes may be included in the company's submission provided sufficient rationale is given to support direct health effects for patients. No changes to the scope required.
	Myeloma UK	These outcome measures capture the most important health related benefits of the treatment.	Comments noted. No action required.
	Napp Pharmaceuticals	Yes	Comments noted. No action required.
	UK Myeloma Forum	Yes. Overall survival is critical. In addition progression free, response rates, adverse effects of treatment and health related quality of life are appropriate outcome measures.	Comments noted. No action required.
Economic analysis	Celgene	No comments	Comments noted. No action required.
	Myeloma UK	We welcome the work of Celgene in the lead up to this re-appraisal and their willingness to bring a patient access scheme to the table for Imnovid. We are confident that the work that has been done since the last appraisal,	Comments noted. No action required.

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		including additional evidence collection, is enough to demonstrate the value of Imnovid to the NHS and to make this important treatment available to myeloma patients.	
	Napp Pharmaceuticals	Bendamustine is now available to the NHS at a price 25% lower than that listed in BNF 70. Furthermore by the time this appraisal commences in full, generic bendamustine will also be available. We believe that it would be important, not only, to take this into account, but also to note please that tender procurement prices will be available later this year. This has implications on the price used in the determination of cost-effectiveness, so we would recommend that the true acquisition price through the tender process should be included by the manufacturer in any health economic modelling.	Comments noted. When there are nationally available price reductions, for example for medicines procured for use in secondary care through contracts negotiated by the NHS Commercial Medicines Unit, then the reduced price should be used in the reference-case analysis to best reflect the price relevant to the NHS. For more details, please see sections 5.5.1–5.5.2 of NICE's guide to the methods of technology appraisal (2013).
	UK Myeloma Forum	Agree regarding appropriate time horizon.	Comments noted. No action required.

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Equality and Diversity	Celgene	No comments	Comments noted. No action required.
	Myeloma UK	Myeloma UK considers equalities information to be covered within the scoping document.	Comments noted. No action required.
	UK Myeloma Forum	There are no equality issues for this therapy.	Comments noted. No action required.
Other considerations	Celgene	No comments	Comments noted. No action required.
	Myeloma UK	No comments	Comments noted. No action required.
Innovation	Celgene	Pomalidomide is an oral therapy and therefore can be self-administered at home, with only outpatient consultations during the course of treatment. This reduces the treatment burden and is particularly important for patients with multiple myeloma who are often frail, elderly and have mobility problems related to their condition. This benefit is unlikely to be fully reflected in the standard QALY measure. Pomalidomide provides a more convenient, once-daily treatment option for patients compared with PBD or bendamustine which require parenteral or subcutaneous administration in a hospital setting. Pomalidomide oral therapy also confers an HRQL advantage, as patients are more able to conduct their daily routine due to fewer hospital visits. Wider impacts include reduced burden to patient's families and informal carers from frequent hospital appointments for treatment administration.	Comments noted. The potential innovative nature of the technology will be considered by the appraisal committee.

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		Pomalidomide can also be prescribed 3 monthly for all patients of non-childbearing age, again reducing the burden to patients, carers and dispensing pharmacies.	
	Myeloma UK	Myeloma UK considers Imnovid to be a very innovative drug and patients who have received it through clinical trials, the Cancer Drugs Fund and in Scotland and Wales report that it is well tolerated and impacts significantly on progression free and overall survival. The clinical trial data from both the NIMBUS and STRATUS studies also demonstrates that it is an extremely effective drug in relapsed and refractory patients. Imnovid was previously available in England via the Cancer Drugs Fund, and was a routine treatment option for multiply relapsed patients during this time. As Imnovid was removed from the Fund, consideration of the drug by NICE for inclusion into routine baseline commissioning is very welcome for Myeloma UK, patients and their families. This is particularly pertinent as beyond currently approved NICE guidance there are no routinely standard of care, which makes it an area of unmet need for patients.	Comments noted. The potential innovative nature of the technology will be considered by the appraisal committee.
	UK Myeloma Forum	Yes. This is a next generation immunomodulatory agent, with evidence to support its use in those who are refractory to other agents in this class (thalidomide and lenalidomide). It is an oral agent which is well tolerated and only requires attendance at hospital 1 -2 / month in comparison to intravenous / subcutaneous administered therapies and those associated with greater toxicity. The data available to aid this appraisal comprises the only published Phase 3 clinical trial (MM-003) in patients who are refractory to both a proteasome	Comments noted. The potential innovative nature of the technology will be considered by the appraisal committee.

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		inhibitor and the available immunomodulatory agents (thalidomide or lenalidomide).	
NICE Pathways	Celgene	As an option after 2 or more prior therapies.	Comments noted. No action required.
	UK Myeloma Forum	It is likely that the technology would fit into the current NICE pathway for patients who are no longer suitable to receive bortezomib or lenalidomide. This would be at 3rd line or 4th line in the current NICE treatment pathway.	Comments noted. No action required.
Questions for consultation	Celgene	*Is pomalidomide likely to be used for treating multiple myeloma after 2 prior therapies in clinical practice? For people previously treated with 2 prior therapies, specifically lenalidomide and bortezomib, is retreatment with lenalidomide used in clinical practice in the NHS?* Pomalidomide could be used after 2 prior therapies. Lenalidomide re-treatment could be feasible, but there is no data to support this and it is not standard clinical practise at this time. *Is retreatment with bortezomib part of established NHS practice for treating multiple myeloma after 3 or more prior therapies?* Retreatment with bortezomib is not standard practise at this line and clinicians can access it as part of the PBD combination. *Have all relevant comparators for pomalidomide been included in the scope?* Yes – please note comments on the comparator section.	Comments noted. No action required.

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		Which treatments are considered to be established clinical practice in the NHS for relapsed and refractory multiple myeloma previously treated with lenalidomide and bortezomib? Pomalidomide when funded via old CDF was established clinical practise. Now pomalidomide is no longer funded, bendamustine used off label is the established clinical practise at this line. *Are the outcomes listed appropriate?* *Are there any subgroups of people in whom pomalidomide is expected to be more clinically effective and cost effective or other groups that should be examined separately?* The outcomes are appropriate and there are no specific subgroups.	
	Myeloma UK	1. Imnovid is likely to be used (as it was done prior to CDF removal) mostly as a fourth line treatment – where patients have had (1) thalidomide based treatment (2) bortezomib based treatment (3) lenalidomide based treatment. However, given the individual and heterogeneous nature of myeloma there may be certain circumstances where patients need to access Imnovid after two prior therapies (particularly if Revlimid is approved at first relapse by NICE) or even after four prior therapies (now Farydak has been approved). If Imnovid is approved, doctors will be able to use their clinical judgement to determine which order the currently available treatments are used in patients, depending on individual need. 2. Lenalidomide and dexamethasone is given on a treatment until progression	Comments noted. No action required.

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		basis, so at this stage (i.e. when they stop responding) patients are considered refractory to lenalidomide. Retreatment with lenalidomide is therefore not routinely done on the NHS and there is no funding available for patients to try this. There may be circumstances where patients respond to Revlimid again – for example if a further drug is added into the combination, but this isn't something that currently happens on the NHS. 3. Velcade retreatment, until recently, has not routinely commissioned on the NHS for patients after three or more prior therapies. The NICE approval of Farydak has allowed retreatment with Velcade to be prescribed in patients (it is currently being prevented elsewhere in the Pathway by NHS England), which is still embedding into clinical practice. Retreatment with Velcade very much depends on a patient's response to Velcade when they first received it, although the addition of Farydak can help retrieve a response to Velcade in myeloma patients.	
Additional comments on the draft scope	UK Myeloma Forum	In answer to the questions posed in the Questions for Consultation section of the scope. 1. Lenalidomide retreatment is not appropriate. According to its marketing authorisation it is administered until the development of progressive disease or toxicity. 2. Bortezomib retreatment after 3 or more therapies would only be considered when supported by TA380 in those who did not have unacceptable toxicity. Bortezomib retreatment otherwise is not funded in the UK 3. All the relevant comparators have been listed above. 4. The outcomes as stated are appropriate	Comments noted. No action required.

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		5. There are no specific subgroups that would require separate evaluation however it should be noted that the activity of pomalidomide for genetically high risk subgroups of myeloma is significant. 6. Pomalidomide would fit in the NICE pathway in those patients with relapsed and refractory disease and who have previously been treated with bortezomib and lenalidomide regimens. This would place it as a 3rd line or 4th line therapy. 7. There are no equal opportunity issues with the use of pomalidomide or myeloma at this stage of therapy	

The following consultees/commentators indicated that they had no comments on the draft scope:

- Department of Health