National Institute for Health and Care Excellence

Single Technology Appraisal (STA)
Daratumumab in combination with bortezomib and dexamethasone for treating relapsed or refractory multiple myeloma

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 scope

Section	Consultee/ Commentator	Comments [sic]	Action
Wording	Janssen-Cilag	Janssen considers the wording of the remit to be appropriate	Comment noted. No action required.
	UK Myeloma Forum	The wording is broadly appropriate. It is important to include the NICE recommended / available choices for therapy at 1st line in the background as this influences choices at subsequent lines	Comment noted. The scope normally includes all treatment options at the lines of therapy relevant to the appraisal. No action required.
Timing Issues	Janssen-Cilag	No comment	Comment noted. No action required.
	UK Myeloma Forum	As myeloma remains incurable and patients continue to die of refractory relapse, this appraisal is urgent. Real world data demonstrates that only 38% of patients from diagnosis reach third line of therapy (Yong at al BJH	Comment noted. No action required.

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		2016).There is a need to rapidly introduce effective therapies to help prolong disease control and overall survival.	

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Background information	Janssen-Cilag	It is important to note that whilst bortezomib is recommended as an option for people at first relapse, its use is restricted by NHSE to people who have not previously received bortezomib.	Comment noted. The scope has been updated to reflect this comment.
	UK Myeloma Forum	The treatment choices recommended / available at first line are missing. Myeloma patients who require a 1st line therapy are stratified according to whether they are transplant eligible (TE) or not transplant eligible (NTE). There is NICE guidance for both these patient groups: TA311 for TE patients recommends bortezomib based therapy (eg bortezomib / thalidomide / dexamethasone) prior to autologous transplant. TA228 for NTE patients recommends thalidomide based therapy at 1st line. Additionally, a significant proportion of NTE patients will receive bortezomib based therapy (e.g. bortezomib / melphalan / prednisolone) following NHSE advice to local commissioners. Overall, it is estimated that 65 – 80% of newly diagnosed myeloma patients, both TE and NTE, in England will receive bortezomib based therapy at 1st line. The use of bortezomib as 2nd line therapy as per TA129 is considered for those patients who either did not receive 1st line bortezomib and are not suitable for carfilzomib (TA457) or were not refractory to 1st line bortezomib and did not experience prohibitive toxicity (e.g. peripheral neuropathy). It	Comment noted. The scope normally includes all treatment options at the lines of therapy relevant to the appraisal. The scope has been updated to reflect the caveats associated with bortezomib re-treatment.

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		should be noted that according to TA457 only those patients who have not previously received bortezomib are eligible for carfilzomib – this is estimated as 20 – 35% of myeloma patients at 2nd line. Not all of these patients (several will be too frail) will be able to receive carfilzomib). Treatment related AE's reported in trials (ASPIRE, ENDEAVOR), potential for cardiac toxicity and twice weekly intravenous use limits application of this therapy. There are a significant proportion of myeloma patients who currently do not have a NICE approved option at 2nd line (those who received 1st line bortezomib and are not suitable or cant access 2nd line bortezomib). This may be up to 75% or more of patients at 2nd line. This is clearly an area of unmet need, that requires urgent attention. It must also be recognised that the CASTOR trial that forms the basis of the evidence for the daratumumab combination therapy under appraisal excluded patients who had failed or were intolerant of bortezomib therapy.	
The technology/ intervention	Janssen-Cilag	No comment	No action required.
	UK Myeloma Forum	The technology is appropriately described	Comment noted. No action required.
Population	Janssen-Cilag	No comment	No action required.
	UK Myeloma Forum	The population would more accurately be described as patients who have had at least 1 prior line of therapy and who are eligible to receive bortezomib (i.e. not refractory or intolerant to bortezomib)	Comment noted. The scope defines the population in line with the marketing authorisation of daratumumab in

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			combination with bortezomib and dexamethasone. No action required.
Comparators	Janssen-Cilag	Janssen considers the list of comparators to be complete but consider it important to highlight that at first relapse, both bortezomib and carfilzomib are restricted to bortezomib naïve patients. There are currently no therapies recommended at for bortezomib experienced patients at first relapse.	Comment noted. The scope has been updated to reflect the caveats associated with bortezomib re-treatment.
	UK Myeloma Forum	People with 1 previous therapy: Lenalidomide with dexamethasone is currently not approved and so cannot be a comparator here. Otherwise comparators are as suggested with the caveat as described above regarding bortezomib eligibility. People with 2 previous therapies and beyond: this is likely to be a very small group of patients. Caveats regarding prior bortezomib exposure as above.	Comment noted. The scope has been updated to reflect the caveats associated with bortezomib re-treatment.
Outcomes	Janssen-Cilag	Janssen considers this to be an appropriate set of outcomes	Comment noted. No action required.
	UK Myeloma Forum	Yes. Response rates including MRD negative status. Note achievement of MRD negative status and progression free survival are clinically accepted surrogate markers for overall survival in myeloma	Comment noted. MRD negative status may be reported within

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			response rates. No action required.
Economic analysis	Janssen-Cilag	No comment	No action required.
	UK Myeloma Forum	yes	Comment noted. No action required.
Equality and Diversity	Janssen-Cilag	No comment	No action required.
	UK Myeloma Forum	No equality issues.	Comment noted. No action required.
Other considerations	Janssen-Cilag	No comment	No action required.
Innovation	Janssen-Cilag	Janssen considers daratumumab, as the first in class fully human immunoglobulin G1 kappa (IgG1κ) monoclonal antibody (mAb), is highly innovative and offers patients with a rare and incurable disease the opportunity for deep and durable response and significant extension of life. Daratumumab was granted the Orphan Drug Designation (ODD) for the treatment of MM/plasma cell myeloma by the United States (US) Food and Drug Administration (FDA) on May 8, 2013 and by the European Commission (EC) on July 17, 2013. In addition, daratumumab was granted Fast Track and Breakthrough Therapy Designation by the FDA The innovative mechanism of action is the underlying reason for the increased efficacy compared to current therapies used in r/r MM. Daratumumab has demonstrated efficacy as a single-agent and when used in combination with current therapies offers highly significant improvements in	Comment noted. You are encouraged to describe the innovative nature of the technology in your evidence submission to NICE. No action required.

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		clinical outcomes. Furthermore, as a targeted agent daratumumab does not add to the treatment toxicity burden.	
	UK Myeloma Forum	Daratumumab is extremely innovative – it is the first active monoclonal antibody for myeloma to be considered by NICE and is well tolerated with few side effects beyond infusion related reactions (generally grade 1 or 2) with the first dose. The innovation here is in the use of a monoclonal antibody that is able not only to target and kill myeloma cells, but that can also activate the immune system. This second immunological action is key to the long term disease control that is seen in people whose disease responds, even if only partially, to the technology. This is the first time that such a technology has been made available for people with this incurable cancer. The data to support this appraisal is from the published CASTOR trial (Palumbo et al. New England Journal of Medicine 2016;375;754-66	Comment noted. You are encouraged to describe the innovative nature of the technology in your evidence submission to NICE. No action required.
Questions for consultation	Janssen-Cilag	It is proposed that daratumumab will fit into the existing NICE pathway for blood and bone marrow cancers in the treatment of adult patients with multiple myeloma who have received at least 1 prior therapy.	Comment noted. No action required.
	UK Myeloma Forum	Treatments considered standard are detailed in the background comments. Outcomes and subgroups are appropriately detailed except as per comments above We would consider daratumumab should be available for patients in accordance with its marketing authorisations in combination with bortezomib, lenalidomide or as a monotherapy.	Comment noted. No action required.

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Additional comments on the draft scope	Janssen-Cilag	No additional comments	No action required.

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

Amgen
Celgene
Department of Health