National Institute for Health and Care Excellence

Health Technology Evaluation

Daratumumab with lenalidomide and dexamethasone for untreated multiple myeloma when stem cell transplant is unsuitable

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
Wording	Janssen-Cilag (manufacturer)	Janssen considers the wording of the remit to be appropriate, aside from the wording to describe the population To align with the licensed wording, Janssen suggest that the population is described as adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant (see Comment 2 below for further details).	Comment noted. The population described in this section of the scope is appropriate and reflects the population in the marketing authorisation. This intervention will be appraised within its marketing authorisation. No changes required.
	Myeloma UK	Yes [wording is appropriate]	Comment noted. No action required.
	UK MYELOMA FORUM	This is a timely appraisal. The addition of monoclonal antibodies (such as Daratumumab) to existing treatments is clearly a step change in treatment. Myeloma remains incurable. This appraisal addresses an important new technology to extend survival.	Comment noted. No action required.

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Timing Issues	Myeloma UK	The COVID-19 pandemic has caused a backlog in overall cancer diagnosis. This is because of a number of factors and the full impact is still to be evaluated but we are expecting an increase in rates of diagnosis for myeloma. Many of these newly diagnosed patients will be in the patient population covered in this appraisal and could be eligible for this treatment if approved. Delivering fast access to the latest and most effective new treatments remains a key part NICE overall strategy. We would therefore like to see this appraisal proceed as quickly and robustly as possible to ensure that as many patients as possible may benefit from this treatment.	Comment noted. This appraisal has been scheduled into the technology appraisals work programme. No action required.
	UK MYELOMA FORUM	This is urgent – there is a need to rapidly introduce effective therapies to help prolong disease control and overall survival. Transplant eligible patients are now able to gain benefit from Daratumumab given in addition to BTD. If successful, this appraisal would allow transplant ineligible myeloma patients to gain the benefit of Daratumumab in combination with Lenalidomide in the upfront setting.	Comment noted. This appraisal has been scheduled into the technology appraisals work programme. No action required.

Comment 2: the draft scope

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Background information	UK MYELOMA FORUM	The description of therapies available is correct.	Comment noted. No action required.

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The technology/ intervention	Janssen-Cilag (manufacturer)	This section of the draft scope only refers to an intravenous formulation, however, on 4th June 2020, daratumumab received European Commission (EC) approval for a subcutaneous (SC) licence extension based on the registrational Phase III Columba study. Janssen request that the description of the technology is updated to also refer to the SC method of administration.	Comment noted. The scope has been updated to include reference to the subcutaneous mode of administration.
	Myeloma UK	Yes [described appropriately]	Comment noted. No actions required.
	UK MYELOMA FORUM	TA is appropriately described. In clinical practice Daratumumab is now given as a subcutaneous infusion rather than as an intravenous infusion, reducing the time it takes to administer this drug. The appraisal should reflect this change in clinical practice.	Comment noted. The scope has been updated to include reference to the subcutaneous mode of administration.
Population	Janssen-Cilag (manufacturer)	To align with the licensed wording, Janssen suggest that the population is described as 'adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant.' Janssen note that this would also align the description of the population with TA763 for transplant eligible multiple myeloma.	Comment noted. The population described in this section of the scope is appropriate and reflects the population in the marketing authorisation. This intervention will be appraised within its marketing authorisation. No changes required.

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	Myeloma UK	Yes [described appropriately]	Comment noted. No action required.
	UK MYELOMA FORUM	Population is correctly defined as adults with untreated myeloma when a stem cell transplant is unsuitable.	Comment noted. No action required.
Comparators	Janssen-Cilag (manufacturer)	Janssen understand that thalidomide-based combinations with an alkylating agent and corticosteroid (eg MPT/ CTd) are now only rarely used in clinical practice in England following the availability of bortezomib-based treatments and lenalidomide with dexamethasone. Therefore, Janssen does not consider thalidomide with an alkylating agent to be best alternative care in current NHS practice. Lenalidomide plus dexamethasone is considered to represent the primary comparator for this appraisal, used by the majority of frontline patients who are ineligible for transplant.	Comment noted. We note your comments, however thalidomide is a recommended treatment. According to NICE's method guide, all potentially relevant comparators should be identified. The committee will take into consideration the relevant comparator(s) based on current NHS clinical practice. No changes to the draft scope required.
	Myeloma UK	Yes – as we understand currently Lenalidomide plus dexamethasone is the current standard of care for newly diagnosed patients who are unsuitable for a transplant.	Comment noted. No action required.
	UK MYELOMA FORUM	This NICE Technology Appraisal assumes most people receive Thalidomide, and if they are unable to tolerate Thalidomide or have contraindications they receive a Bortezomib based regimen or Lenalidomide dexamethasone.	Comment noted. We note your comments, however thalidomide is a recommended treatment. According to

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		In clinical practice most patients receive Lenalidomide Dexamethasone. Some patients may receive Bortezomib with an alkylator and corticosteroid due to high risk genetics (such as TP53 deletion) or because there is an urgent need to recover renal function in those presenting with renal impairment. Thalidomide is not given in clinical practice to this group of patients, and is therefore not an appropriate comparator.	NICE's method guide, all potentially relevant comparators should be identified. The committee will take into consideration the relevant comparator(s) based on current NHS clinical practice. No changes to the draft scope required.
Outcomes	Janssen-Cilag (manufacturer)	Janssen consider that the outcomes section of the scope should be extended to include minimal residual disease (MRD) negativity rate which is now recommended in International Myeloma Working Group (IMWG) clinical practice guidelines. MRD negativity was also included as an outcome in the final scope for a similar daratumumab indication in the untreated multiple myeloma population (TA763).	Comment noted. Minimal residual disease (MRD)-negative status has been added to the outcomes section of the scope.
	Myeloma UK	Yes [described appropriately]	Comment noted. No action required.
	UK MYELOMA FORUM	Yes. Response rates including MRD status	Comment noted. No action required.
Innovation	Janssen-Cilag (manufacturer)	There is an urgency to use the most effective treatments for MM in the frontline setting, as patients may not benefit from subsequent treatment lines due to high attrition rates in MM.	Comment noted. The committee will consider whether daratumumab

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		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. Janssen considers the use of daratumumab in the frontline setting, as the first in class fully human immunoglobulin G1 kappa (IgG1κ) monoclonal antibody (mAb), to be highly innovative and offers a significant and substantial impact for the entire MM pathway in the UK. Daratumumab operates through a novel mechanism of action shown in vitro to effectively induce CD38+ cell death through multiple diverse immune-mediated mechanisms and apoptosis. The innovative multifactorial mechanism of action is the underlying reason for the increased efficacy and broader therapeutic effect compared to currently available therapies used at all stages in the MM pathway. Daratumumab has demonstrated efficacy as a single-agent, and when used in combination with current therapies, offers highly significant improvements in clinical outcomes, as observed in UK clinical practice. Furthermore, as a targeted agent daratumumab does not add to the treatment toxicity burden. Adding daratumumab to frontline standard of care NHS treatments significantly reduces the risk of progression or death for all newly diagnosed MM patients. Janssen consider the combination of daratumumab with lenalidomide and dexamethasone (DLd) to be a landmark advance in the clinical management of patients with transplant ineligible newly diagnosed MM, as:	is innovative. No action required.

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		• DLd is the only triplet regimen which is licensed for continuous use to suppress residual disease and extend the period of first remission in this patient population. • This specific combination benefits from the synergistic immune-mediated relationship between daratumumab and IMiDs such as lenalidomide. DLd offers patients with an uncurable disease the opportunity for a deep and durable response leading to significant extension of life compared to currently available NHS standard therapies.	
	Myeloma UK	In past appraisals Daratumumab has been defined by NICE as innovative and it has become a significant treatment in the myeloma treatment pathway. Currently patients who are newly diagnosed and ineligible for a stem cell transplant may only receive this treatment at a further line in the treatment pathway if it is available through the CDF. The potential for this patient population to receive daratumumab at this point in the pathway would see it remain as an innovative treatment.	Comment noted. The committee will consider whether daratumumab is innovative. No action required.
	UK MYELOMA FORUM	Daratumumab is an innovative technology. The addition of Daratumumab is available to patients with untreated myeloma who are eligible for stem cell transplantation (TA763). This added benefit of Daratumumab is not currently available to patients who can not receive high dose chemotherapy. Importantly, the addition of Daratumumab to standard of care (Lenalidomide Dexamethasone) improves overall survival and prolonged PFS (Facon et al, Lancet Oncology November 2021). This is a step change for this group of patients who gain most from initial treatment and have less chance of benefiting from treatment at relapse (due to age, frailty and associated co-morbidity).	Comment noted. The committee will consider whether daratumumab is innovative. No action required.

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Questions for consultation	Janssen-Cilag (manufacturer)	**Have all relevant comparators for daratumumab with lenalidomide and dexamethasone been included in the scope?** • **Which treatments are considered to be established clinical practice in the NHS for untreated multiple myeloma when stem cell transplant is unsuitable**? Please see comments on comparators above. **Are the outcomes listed appropriate?** Please see comments on the outcomes section above. **Are there any subgroups of people in whom daratumumab with lenalidomide and dexamethasone is expected to be more clinically effective and cost effective or other groups that should be examined separately?** No subgroups have been identified for which daratumumab in combination with lenalidomide and dexamethasone is expected to be more clinically effective and cost effective. Janssen do not believe there are any other groups that should be examined separately. **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 daratumumab with lenalidomide and dexamethasone is licensed;** • **could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider**	Comments noted. Please see relevant responses in other sections of this document.

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		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.** No comments **Do you consider daratumumab with lenalidomide and dexamethasone 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)?** Please see comments on innovation above. **Do you consider that the use of daratumumab with lenalidomide and dexamethasone can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?** Please see comments on innovation above**.**	
	UK MYELOMA FORUM	Certain subgroups may have an added benefit. Those patients with poor risk cytogenetic features may have a higher response rate.	Comment noted. The committee can consider relevant subgroups

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			where data is available. No action required.