National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Daratumumab in combination for newly diagnosed systemic amyloid light-chain amyloidosis [ID3748]

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	NHS England and Improvement	This is an appropriate referral	Thank you. No action required.
	British Society for Heart Failure	This [referral of the topic to NICE for appraisal] is appropriate. There is no licensed treatment for AL amyloidosis so a considerable unmet need.	Thank you. No action required.
	Janssen-Cilag Ltd.	Yes, it [referral of the topic to NICE for appraisal] is appropriate.	Thank you. No action required.
	Myeloma UK	This will be first NICE appraisal for a treatment directly related to AL Amyloidosis and Myeloma UK considers it appropriate to refer this topic to NICE.	Thank you. No action required.
Wording	NHS England and Improvement	Yes, the remit does address the clinical issues and the cost effectiveness	Thank you. No action required.

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	British Society for Heart Failure	It does [the wording of the remit reflect the issues of clinical and cost effectiveness about this technology or technologies that NICE should consider].	Thank you. No action required.
	Janssen-Cilag Ltd.	The wording of the remit aligns with the expected marketing authorisation. Amyloidosis is a disease with a high unmet need as there are currently no treatments indicated for its treatment. [redacted]	Thank you. No action required.
	Myeloma UK	Myeloma UK considers the remit to reflect the issues of clinical and cost effectiveness.	Thank you. No action required.
Timing Issues	NHS England and Improvement	This appraisal is timely	Thank you for your comment. NICE aims to publish guidance as soon as possible after the company receives the marketing authorisation and introduces the technology in the UK. NICE has scheduled this topic into its work programme.
	British Society for Heart Failure	Treatments which have been licensed for use in myeloma are currently prescribed to patients with AL amyloidosis but despite this, mortality and morbidity remains high. This is urgent.	Thank you for your comment. NICE aims to publish guidance as soon as possible after

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			the company receives the marketing authorisation and introduces the technology in the UK. NICE has scheduled this topic into its work programme.
	Janssen-Cilag Ltd.	Janssen expect license approval from the EMA in [redacted]. The company would like to ask for scheduling in line with a [redacted] submission so that the necessary clinical data are available.	Thank you for your comment. NICE aims to publish guidance as soon as possible after the company receives the marketing authorisation and introduces the technology in the UK. NICE has scheduled this topic into its work programme.
	Myeloma UK	No comment.	Noted. No action required.
Additional comments on the draft remit	NHS England and Improvement	N/A	Noted. No action required.
	British Society for Heart Failure	N/A	Noted. No action required.

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	Janssen-Cilag Ltd.	N/A	Noted. No action required.
	Myeloma UK	N/A	Noted. No action required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	NHS England and Improvement	The background information is accurate. It would be helpful to have more detail regarding the lived experience of this disease.	Thank you for your comment. The background section is intended to provide a broad overview of the disease and its management. No action required.
	British Society for Heart Failure	The background information is accurate. Earlier diagnosis and treatment confers a better prognosis. Cardiac involvement confers a poorer prognosis and is found in about 60% patients.	Thank you for your comment. The background section is intended to provide a broad overview of the disease and its management. No action required.

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	Janssen-Cilag Ltd.	Yes, as mentioned in the section, there are no current licensed treatments for AL amyloidosis and the standard of care is based on the myeloma pathway.	Thank you for your comment. No action required.
	Myeloma UK	We consider this information to be complete and accurate.	Thank you for your comment. No action required.
The technology/ intervention	NHS England and Improvement	The description of the technology is accurate.	Thank you. No action required.
	British Society for Heart Failure	Yes [the description of the technology is accurate].	Thank you. No action required.
	Janssen-Cilag Ltd.	Daratumumab is now available in England as a subcutaneous formulation. This formulation was approved 4 June 2020. The ANDROMEDA trial used a subcutaneous formulation for daratumumab and daratumumab is expected to be administered to systemic AL amyloidosis patients using a subcutaneous formulation in UK clinical practice.	Thank you. The scope has been updated to include subcutaneous formulation.
	Myeloma UK	Yes [the description of the technology is accurate].	Thank you. No action required.
Population	NHS England and Improvement	The definition of the population is accurate.	Thank you. No action required.
	British Society for Heart Failure	Yes [the population is defined appropriately].	Thank you. No action required.

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	Janssen-Cilag Ltd.	No comment.	Noted. No action required.
	Myeloma UK	We consider the population to be appropriately defined.	Thank you. No action required.
Comparators	NHS England and Improvement	The comparators are appropriate.	Thank you. No action required.
	British Society for Heart Failure	Yes [these are the standard treatments currently used in the NHS with which the technology should be compared]. • Bortezomib with dexamethasone, an alkylating treatment and/or immunomodulatory drugs Bortezomib with dexamethasone, an alkylating treatment and/or immunomodulatory drugs**.**	Thank you. No action required.
	Janssen-Cilag Ltd.	Daratumumab underwent NICE early scientific advice in 2016. This advice indicated that cyclophosphamide, bortezomib and dexamethasone (CyBorD), as the most relevant comparator for treating newly diagnosed systemic AL amyloidosis in the UK. English clinical experts estimate over 95% of patients receive CyBorD at frontline. The additional comparators listed in the draft scope are used much less frequently than CyBorD but are nonetheless treatment options in the UK for a small percent of patients. Additionally, a small number of patients who cannot receive CyBorD at frontline will receive lenalidomide with dexamethasone.	Thank you for your comment. The list of relevant comparators has been updated.

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	Myeloma UK	Yes [these are the standard treatments currently used in the NHS with which the technology should be compared].	Thank you. No action required.
Outcomes	NHS England and Improvement	The outcomes are appropriate, the bullet point regarding response rates should include partial haematological response and specific renal and cardiac responses. Relapse rates should also be considered as an outcome measure.	Thank you for your comment. Based on discussion at the scoping workshop, 'organ response rates' have been added to the scope. 'Complete haematologic response' has been adjusted to 'haematologic response rates' responses to encompass other types of responses.
	British Society for Heart Failure	Yes [these outcome measures capture the most important health related benefits (and harms) of the technology].	Thank you. No action required.
	Janssen-Cilag Ltd.	The outcomes listed in the draft scope are appropriate. As systemic AL amyloidosis usually affects multiple organs, 'organ response rate' and 'major organ deterioration progression-free survival' should be included as outcomes of interest.	Thank you for your comment. Based on discussion at the scoping workshop, major organ deterioration progression-free survival has been added to the scope.

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	Myeloma UK	Yes [these outcome measures capture the most important health related benefits (and harms) of the technology].	Thank you. No action required.
Economic analysis	NHS England and Improvement	The economic analysis s reasonable but should take into account the very small patient cohort.	Thank you. No action required.
	British Society for Heart Failure	This time horizon seems appropriate.	Thank you. No action required.
	Janssen-Cilag Ltd.	No comment.	Noted. No action required.
	Myeloma UK	No Comments	Noted. No action required.
Equality and Diversity	NHS England and Improvement	Systemic amyloid light-chain amyloidosis is a very rare disease and patients in England benefit from a single national expert centre which is world leading in this field. We are not aware of any specific access issues relating to people with protected characteristics or that commissioning this drug would disadvantage any groups.	Thank you. No action required.
	British Society for Heart Failure	N/A	Noted. No action required.
	Janssen-Cilag Ltd.	Janssen would like to highlight that a subgroup of patients may face inequality in access depending on the NICE recommendation for this indication. AL amyloidosis patients with level 3b cardiac status were excluded from the ANDROMEDA trial due to their overall fitness levels and poor survival outcomes (median overall survival of 3-4 months). Deemed as high-	Thank you for your comment. Consideration of subgroups based on the severity of cardiac

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		risk patients, they are often excluded from clinical trials and evidence regarding these patients is extremely rare. Cardiac 3b patients have the most severe degree of cardiac involvement. These patients require a rapid response to treatment. The better this response, the better the expected survival. However, in addition to their poor survival outcomes, these patients have limited ability to receive a number of full dose treatments. They perhaps represent the AL amyloidosis patients with the highest unmet need. Although data are limited for this population, there would be an equity issue if these patients were excluded from receiving daratumumab simply because they were too ill to be included in clinical trials.	failure has been added to the scope.
	Myeloma UK	No Comments	Noted. No action required.
Other considerations	NHS England and Improvement	N/A	Noted. No action required.
	British Society for Heart Failure	N/A	Noted. No action required.
	Janssen-Cilag Ltd.	No comment.	Noted. No action required.
	Myeloma UK	No Additional suggestions.	Noted. No action required.
Innovation	NHS England and Improvement	This is an innovative technology. The calculation of QALYs needs to reflect the small number of patients and the benefit to this cohort of the technology.	Thank you for your comment. The company

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			submission can expand on the potential innovative nature of the technology, in particular its potential to make a significant and substantial impact on health-related benefits that are unlikely to be included in the QALY calculation during the assessment. No action required.
	British Society for Heart Failure	The addition of daratumumab (dara) to standard treatment has a huge impact on morbidity and mortality. In the Andromeda trial, over 50% of patients who received dara [sic] in addition to standard therapy CyBorD (cyclophosphamide, dexamethasone and bortezimib [sic]) achieved complete haematological response compared with 20% in CyBorD group. This translated into improved organ function. The combination was well tolerated. This trial has been described as the most significant trial in AL amyloidosis. It is a “gamechanger”.	Thank you for your comment. The company submission can expand on the potential innovative nature of the technology, in particular its potential to make a significant and substantial impact on health-related benefits that are unlikely to be included in the QALY calculation during the assessment. No action required.

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	Janssen-Cilag Ltd.	There are currently no licensed treatments approved for systemic AL amyloidosis. Daratumumab is considered innovative as it will be the first licensed product specifically targeting aspects of the disease and improving outcomes.	Thank you for your comment. The company submission can expand on the potential innovative nature of the technology, in particular its potential to make a significant and substantial impact on health-related benefits that are unlikely to be included in the QALY calculation during the assessment. No action required.
	Myeloma UK	Daratumumab is an innovative technology which we consider having potential to make a significant and substantial impact. This will be the first monoclonal antibody used to treated newly diagnosed patients with AL Amyloidosis and we would consider this a step change in the treatment options for patients. The results from the safety run in phase III Andromeda trial shows that this is a relatively non-toxic but highly effective treatment for patients with AL Amyloidosis.	Thank you for your comment. The company submission can expand on the potential innovative nature of the technology, in particular its potential to make a significant and substantial impact on health-related benefits that are unlikely to be included in the QALY calculation during the

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			assessment. No action required.
Questions for consultation	NHS England and Improvement	N/A	Noted. No action required.
	British Society for Heart Failure	N/A	Noted. No action required.
	Janssen-Cilag Ltd.	**Have all relevant comparators for daratumumab been included in the scope? Which treatments are considered to be established clinical practice in the NHS newly diagnosed systemic amyloid light-chain amyloidosis? How should best supportive care be defined? Is stem cell transplant a relevant comparator – is the population likely to be eligible for treatment with daratumumab similar to the population eligible for a stem cell transplant?** Please see comments on comparators above. CyBorD is considered established clinical practice and estimated to be received by over 95% of frontline patients. Best supportive care for systemic AL amyloidosis comprises of renal and/or heart failure treatment dependent on an individual's organ involvement. Due to the difficulty of diagnosing AL amyloidosis, patients are often diagnosed rather late and require a rapid response. Additionally, organ damage is usually present by the point of diagnosis. Due to these factors, ASCT is rarely used as frontline treatment. Very rarely are there patients in the UK who are fit enough to receive ASCT at frontline. **Are the outcomes listed appropriate?**	Thank you for your comment. No action required.

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		Please see comments on outcomes above. **Are there any subgroups of people in whom daratumumab 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 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 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.** Please see comments on equality above.	

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		Do you consider daratumumab 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 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.** Please see innovation section above. **To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly.** Janssen do not consider that there will be any barriers to adoption.	
	Myeloma UK	Treatment of AL amyloidosis is based on anti-myeloma therapy but there is no standard treatment and it has to be tailored to the individual patient in terms of their age, comorbidities, extent of organ involvement and patient's wishes with the treatment goal to achieve a very good partial response or better, if possible. First line treatment is recommended with combination chemotherapy regimens similar to those used in myeloma but typically using dexamethasone. About one fifth of newly diagnosed patients with AL amyloidosis may be suitable for consideration of high dose intravenous chemotherapy as first-line treatment.	Thank you for your comment. No action required.

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		There is greater treatment-related toxicity in patients with AL amyloidosis compared to that seen in patients with multiple myeloma and dose reductions are required. Daratumumab represents the first NICE appraisal for a treatment directly related to AL Amyloidosis. This will be the first monoclonal antibody used in the treatment of AL Amyloidosis.	
Additional comments on the draft scope	NHS England and Improvement	N/A	Noted. No action required.
	British Society for Heart Failure	N/A	Noted. No action required.
	Janssen-Cilag Ltd.	No additional comments.	Noted. No action required.
	Myeloma UK	N/A	Noted. No action required.

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

None.