National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Isatuximab with pomalidomide and dexamethasone for treating relapsed or refractory multiple myeloma [ID1477]

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
Wording	UK Myeloma Forum	The remit is appropriate	Comment noted. No action required.
	Sanofi UK	The wording of the remit is appropriate.	Comment noted. No action required.
	Janssen-Cilag Limited	No comment	No action required.
Timing Issues	UK Myeloma Forum	Following marketing authorisation approval there is an urgency to provide access to this combination treatment – there is an unmet need for effective therapies for patients with relapsed and refractory myeloma	Comment noted. NICE schedules technology appraisals so that guidance to the NHS is timely. For cancer drugs, NICE aims to publish final guidance within 90 days of

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			marketing authorisation wherever possible. No action required.
	Sanofi UK	There is high unmet need in patients with relapsed/refractory multiple myeloma (RRMM). Life expectancy is poor; ranging from 8 to 12 months[1] and treatment options are limited. For patients failing at least 2 or more prior therapies, including mainstay treatment (a proteasome inhibitor with or without lenalidomide), the clinical need is particularly high as current treatment options available for routine commissioning, offer progression-free survival gains of 4-5 months but may be limited by toxicity[2]. A NICE appraisal process closely aligned with the regulatory timings discussed below will ensure that patients who meet the intended label population will have access to an alternative effective, licenced treatment option. 1. Usmani S, Ahmadi T, Ng Y, et al. Analysis of Real-World Data on Overall Survival in Multiple Myeloma Patients With >/=3 Prior Lines of Therapy Including a Proteasome Inhibitor (PI) and an Immunomodulatory Drug (IMiD), or Double Refractory to a PI and an IMiD. *Oncologist*. 2016. 2. NICE. (2018). Daratumumab monotherapy for treating relapsed and refractory multiple myeloma. [online]. Available at: https://www.nice.org.uk/guidance/ta510/documents/committee-papers [Accessed 07 Mar. 2019]	Comment noted. NICE schedules technology appraisals so that guidance to the NHS is timely. For cancer drugs, NICE aims to publish final guidance within 90 days of marketing authorisation wherever possible. No action required.
	Janssen-Cilag Limited	No comment	No action required.

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Additional comments on the draft remit	UK Myeloma Forum	None	No action required.
	Janssen-Cilag Limited	No comment	No action required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	UK Myeloma Forum	The background is accurate	Comment noted. No action required.
	Sanofi UK	The background information provided is accurate. For completeness, we would add that the brand name for isatuximab is [redacted]	Comment noted. No action required.
	Janssen-Cilag Limited	No comment	No action required.
The technology/ intervention	UK Myeloma Forum	The description is accurate	Comment noted. No action required.
	Sanofi UK	The description is accurate.	Comment noted. No action required.
	Janssen-Cilag Limited	No comment	No action required.

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Population	UK Myeloma Forum	The population is define appropriately	Comment noted. No action required.
	Sanofi UK	The population is defined appropriately.	Comment noted. No action required.
	Janssen-Cilag Limited	No comment	No action required.
Comparators	UK Myeloma Forum	The comparators should also include daratumumab monotherapy for those who have received 3 prior lines of therapy	Comment noted. Daratumumab monotherapy is recommended for use within the Cancer Drugs Fund. CDF treatments are not included as comparators in scopes as they do not meet the definition of 'established NHS practice', one of the prerequisite factors when selecting comparators as part of the scoping process. No action required.
	Sanofi UK	The comparators identified in the scope are relevant at the present time. However, ongoing reviews by NICE on potential comparators in RRMM could impact isatuximab's place in therapy.	Comment noted. Daratumumab monotherapy is recommended for use

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		3rd line setting • Currently, another combination treatment, panobinostat + bortezomib + dexamethasone is recommended by NICE for patients who have had 2 previous therapies[1]. It is considered effective but its use may be limited due to toxicity[2]. Usage in the UK is approximately 2-3% at this line of therapy[3]. • The isatuximab registration study (ICARIA) was performed in patients who had failed lenolidomide. The anticipated licence is likely to reflect the patient population in the ICARIA study. Therefore, although lenalidomide may be considered standard of care at 3rd line, it would not be considered a comparator for this appraisal. **4th line setting** • For patients who have had 3 or more prior therapies, pomalidomide plus dexamethasone is recommended by NICE. This combination is the comparator in the isatuximab registration study, ICARIA. • We would also highlight that at 4th line, daratumumab monotherapy is widely used, despite its use being limited to CDF[4]. Market research data from Sept/Oct 2018 suggest almost 40% use of daratumumab in the 4th line setting[3]. 1. NICE. (2016). Panobinostat for treating multiple myeloma after at least 2 previous treatments. [online] Available at: https://www.nice.org.uk/guidance/ta380 [Accessed 25 Feb. 2019] 2. NICE. (2018). Daratumumab monotherapy for treating relapsed and refractory multiple myeloma. [online]. Available at:	within the Cancer Drugs Fund. CDF treatments cannot be labelled 'established NHS practice', one of the prerequisite factors when selecting comparators as part of the scoping process. No action required.

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		https://www.nice.org.uk/guidance/ta510/documents/committee-papers [Accessed 07 Mar. 2019] 3. Sanofi Market research, Sept/Oct 2018 4. NICE. (2018). Daratumumab monotherapy for treating relapsed and refractory multiple myeloma. [online] Available at: https://www.nice.org.uk/guidance/ta510 [Accessed 25 Feb. 2019]	
	Janssen-Cilag Limited	In addition to the comparators already listed, NICE TA171 recommends lenalidomide in combination with dexamethasone (Rd) as an option for the treatment of multiple myeloma for people who have received two or more prior therapies (i.e. Rd should be included as a comparator at second-line and third-line)	Isatuximab in combination with pomalidomide and dexamethasone is being studied for relapsed and refractory multiple myeloma in adults who have received at least 2 lines of prior therapies, including lenalidomide and a proteasome inhibitor. Therefore, lenalidomide has not been included as a comparator in the scope as people are unlikely to be retreated with lenalidomide. No action required.
	Celgene	The following potentially relevant comparators funded via the Cancer Drugs	Comment noted.

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		Fund have been omitted; • Daratumumab monotherapy for people who have had 3 prior therapies • Bendamustine for people who have had 3 or more prior therapies (not appraised by NICE; does not currently have a marketing authorisation in the UK for this indication)	CDF treatments (daratumumab) do not meet the definition of 'established NHS practice', and are therefore excluded as comparators in the scope. Previous technology appraisals (TA510) have determined that bendamustine does not reflect established NHS practice in England for fourth- and subsequent-line treatment of relapsed or refractory multiple myeloma. No action required.
Outcomes	UK Myeloma Forum	yes	Comment noted. No action required.
	Sanofi UK	Time to progression, time-to-next treatment and duration of response are outcomes collected in the isatuximab registration study and should be included in the scope.	Comment noted. The scope has been updated to include the time to progression, time-to-next treatment and duration of

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			response as outcomes.
	Janssen-Cilag Limited	No comment	No action required.
Economic analysis	UK Myeloma Forum	An appropriate time horizon for economic analysis would be for up to a maximum 10 years of survival follow-up due to the uncertainties that exist with this type of analysis	Comment noted. No action required.
	Sanofi UK	The economic analysis will be based on the NICE reference case[1]. 1. NICE Guide to the methods of technology appraisal 2013. Available at: https://www.nice.org.uk/process/pmg9/resources/guide-to-the-methods-of-technology-appraisal-2013-pdf-2007975843781 Accessed: March 2019	Comment noted. No action required.
	Janssen-Cilag Limited	No comment	No action required.
Equality and Diversity	UK Myeloma Forum	There are no equality issues. It would not be acceptable to define subgroups unless there is clear significant benefits apparent as this would lead to inequality of access to treatment	Comment noted. No action required.
	Sanofi UK	No equity issues have been identified.	Comment noted. No action required.
	Janssen-Cilag Limited	No comment	No action required.

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Other considerations	UK Myeloma Forum	Implementation should align with the marketing authorisation rather than at a single specific timepoint (e.g as seen with daratumumab TA510)	Comment noted. The position of treatment in the pathway would normally form part of the committee's discussion. No action required.
	Sanofi UK	1. [redacted] Davis, S. (2014). Assessing technologies that are not cost-effective. [online] NICE Decision Support Unit. Available at: http://nicedsu.org.uk/wp-	Comment noted. No action required.

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		content/uploads/2016/03/Not_CE_at_zero_price_FINAL_14.07.14.pdf [Accessed 25 Feb. 2019].	
	Janssen-Cilag Limited	No comment	No action required.
Innovation	UK Myeloma Forum	This is an extremely innovative technology. It is only recently that antibody therapies have had demonstrated anti-myeloma efficacy. The use of an effective combination of anti-CD38 monoclonal antibody with an immunomodulatory drug exploits complimentary mechanisms of action for a patient group who have limited options and often with a poor outcome. This combination potentially harnesses the anti-myeloma activity of 2 effective treatments with synergistic effect. This will have substantial health related benefits for patients by controlling disease related symptoms – something that is often difficult to quantify in quality of life assessments	Comment noted. You are encouraged to describe the innovative nature of this technology in your submission to NICE. No action required.
	Sanofi UK	Despite the availability of newer treatments which have led to an improvement in patient outcomes; once a patient becomes refractory to those agents, survival is limited and MM remains an incurable disease with life expectancy for relapsed/refractory multiple myeloma (RRMM) between 8-12 months[1,2] . Therefore there is clinical unmet need in RRMM which is particularly high at 4th line (after 3 prior treatments). Currently only pomalidomide is available for routine commissioning in this setting[3]. Daratumumab monotherapy is available only via CDF[4] but increasing usage as per market research emphasises that there is unmet need in the 4th line setting[5]. Increasingly, research is focused on the search for combinations of these novel agents with standard of care in MM, looking for potential synergistic effects.	Comment noted. You are encouraged to describe the innovative nature of this technology in your submission to NICE. No action required.

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		Monoclonal antibodies (MAb) are one of the most promising groups of drugs in development in the treatment of MM with several of them demonstrating activity in this disease[6]. One of the most important characteristics of this type of agents, apart from the clinical efficacy demonstrated, is the safety profile and the absence of potential cross-resistance with other agents currently utilised. This makes MAb an ideal combination partner with proteasome inhibitors, immunomodulatory drugs (IMiDs) and steroids. Isatuximab is a new immunoglobulin (Ig) G1 monoclonal antibody (mAb) that selectively binds to the human cell surface antigen molecule classified as cluster of differentiation (CD) 38. The expression of CD38 is especially notable in MM as >98% of patients are positive for this protein[7, 8] . The effect of pomalidomide on the immune system coupled with the mechanism of action of isatuximab, suggests that the combination of both drugs may improve the benefit seen with pomalidomide in combination with low-dose dexamethasone in RRMM patients whose disease have previously failed to respond to 3 or more anti-myeloma treatments. If recommended, isatuximab in combination with pomalidomide and dexamethasone could offer an effective treatment option for a patient group with a particularly poor prognosis for whom there are few alternatives. The potential impact on patients and their family of having access to a treatment which leads to longer life over currently available treatment in 4th line setting should not be underestimated. Pomalidomide + dexamethasone reports progression-free survival (PFS) of 4 months in its pivotal trial[9], while daratumumab, in a single arm phase II trial, reported a median PFS of 3.7 months[10]. A Phase III trial investigating isatuximab in combination with pomalidomide and dexamethasone has been	

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		completed and while data is not yet available, the trial has met its primary endpoint (PFS). [redacted] The combination of isatuximab, pomalidomide and dexamethasone could represent a step-change in the management of RRMM. The opportunity for further lines of treatment, particularly in the 4th line setting, may offer patients hope and optimism that are not intrinsically captured in QALY but are important in the wider context of the decision-making process. 1. Streetly MJ, Kazmi M, Campbell T and Schey SA. Clinical review of overall survival for myeloma patients progressing after both bortezomib and lenalidomide based therapy. Br J Haematol. 2014; 165:68. 2. Usmani S, Ahmadi T, Ng Y, et al. Analysis of Real-World Data on Overall Survival in Multiple Myeloma Patients With >/=3 Prior Lines of Therapy Including a Proteasome Inhibitor (PI) and an Immunomodulatory Drug (IMiD), or Double Refractory to a PI and an IMiD. *Oncologist*. 2016. 3. NICE (2017). Pomalidomide for multiple myeloma previously treated with lenolidomide and bortezomib. [online] Available at: https://www.nice.org.uk/guidance/ta427 [Accessed 25 Feb, 2019] 4. Daratumumab monotherapy for treating relapsed and refractory multiple myeloma. [online] Available at: https://www.nice.org.uk/guidance/ta510 [Accessed 25 Feb. 2019] 5. Sanofi Market research, Sept/Oct 2018 6. Ocio EM, Mitsiades CS, Orlowski RZ, Anderson KC. Future agents and treatment directions in multiple myeloma. Expert Rev Hematol 2014; 7(1):127-141. 7. Goldmacher VS, Bourret LA, Levine BA, Rasmussen RA, Pourshadi M, Lambert JM, et al. Anti-CD38-blocked ricin: an immunotoxin for the treatment of multiple	

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		myeloma. Blood. 1994; 84(9):3017-25 8. Lin P, Owens R, Tricot G, Wilson CS. Flow cytometric immunophenotypic analysis of 306 cases of multiple myeloma. Am J Clin Pathol. 2004;121(4):482-8. 9. San Miguel J, Weisel K, Moreau P et al. Pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone alone for patients with relapsed and refractory multiple myeloma (MM-003): a randomised, open-label, phase 3 trial. Lancet Oncology 2013;14:1055-66. 10. Lonial S, Weiss BM, Usmani SZ, Singhal S, Chari A, Bahlis NJ, et al. Daratumumab monotherapy in patients with treatment-refractory multiple myeloma (SIRIUS): an open-label, randomised, phase 2 trial. Lancet. 2016;387:1551-60.	
	Janssen-Cilag Limited	No comment	No action required.
Questions for consultation	UK Myeloma Forum	We would suggest daratumumab should also be considered a comparator. In terms of the NICE clinical pathway for myeloma the isatuximab pomalidomide dexamethasone combination should be considered for those patients who have relapsed and/or refractory myeloma and have previously received a proteasome inhibitor and an immunomodulatory agent (lenalidomide). This could potentially position the treatment under consideration as a 3rd line or 4th line therapy. The other questions for consultation have been answered above	Comment noted. Daratumumab monotherapy is recommended for use within the Cancer Drugs Fund. CDF treatments cannot be labelled 'established NHS practice', one of the prerequisite factors when selecting comparators as part of the scoping process. No action required.

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	Sanofi UK	• **Are there any subgroups of people in whom isatuximab in combination with pomalidomide and dexamethasone is expected to be more clinically effective and cost effective or other groups that should be examined separately?** The following subgroups are pre-specified in the ICARIA trial and will be examined separately: - 2 or 3 lines of therapy - >3 lines of therapy - Age - Renal function - ISS Staging - Cytogenetic risks • **Where do you consider isatuximab in combination with pomalidomide and dexamethasone will fit into the existing NICE pathway, 'Myeloma'?** In line with its anticipated licence, and current treatment options recommended by NICE [redacted] • **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**	Comments noted. No action required.

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		We do not anticipate barriers to the adoption of this technology into practice. • **NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process.** STA process is appropriate as it will result in timely guidance to the NHS. [redacted]. • **Would it be appropriate to use the cost comparison methodology for this topic? Is the new technology likely to be similar in its clinical efficacy and resource use to any of the comparators?** No, cost comparison method is not appropriate as the clinical efficacy is not similar, nor is the resource use between isatuximab and its comparators. • **Is the primary outcome that was measured in the trial or used to drive the model for the comparator(s) still clinically relevant?** The primary endpoint is progression-free survival and key secondary endpoints include overall response rate and overall survival. All these are well established and accepted outcome measures in oncology HTAs and considered clinically relevant. • **Is there any substantial new evidence for the comparator**	

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		technology/ies that has not been considered? Are there any important ongoing trials reporting in the next year? To the best of our knowledge there is no new evidence expected in the next year that will be relevant to the population defined in the scope. However, a number of changes to the treatment pathway for RRMM are expected where treatments seek reimbursement at earlier lines of therapy. This may impact the place of isatuximab in the pathway. **1.** Davis, S. (2014). Assessing technologies that are not cost-effective. [online] NICE Decision Support Unit. Available at: **http://nicedsu.org.uk/wp-content/uploads/2016/03/Not_CE_at_zero_price_FINAL_14.07.14.pdf** [Accessed 25 Feb. 2019].	
	Janssen-Cilag Limited	No comment	No action required.
Additional comments on the draft scope	UK Myeloma Forum	There is an unmet need for truly effective therapies that gain an overall response for the majority of patients and have significant durability of disease control following relapse after a proteasome inhibitor and lenalidomide which is reflected in the poor overall survival observed from this timepoint. It becomes increasingly difficult for patients to tolerate multiple lines of therapy after this point and the use of a well tolerated combination of effective therapies offers a potential for significantly better disease control than is currently observed which is associated with significantly better quality of life and duration of life for these patients. It should also be considered whether or not this treatment qualifies for end of life criteria due to the proposed positioning of the treatment. The committee has a real opportunity to positively impact on a large number of myeloma patients by approving this	Comment noted. You are encouraged to describe the innovative nature of this technology in your submission to NICE. The appraisal committee will consider whether this technology meets the criteria for life-extending treatments at the end of

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		technology / therapy combination.	life during the course of the appraisal. No action required.
	Janssen-Cilag Limited	No comment	No action required.

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

Myeloma UK