National Institute for Health and Care Excellence

Health Technology Evaluation

Isatuximab in combination for untreated multiple myeloma when a stem cell transplant is unsuitable [ID3981]

Response to stakeholder organisation comments on the draft remit and draft scope

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 and proposed process

Section	Stakeholder	Comments [sic]	Action
Appropriateness of an evaluation and proposed evaluation route	Sanofi	Sanofi believes that the evaluation is both appropriate and necessary given the potential of isatuximab to significantly improve outcomes for patients with newly diagnosed multiple myeloma (NDMM) [redacted]. Sanofi is also in agreement with the proposed evaluation route.	Thank you for your comment. No changes to the scope required.
	Myeloma UK	Yes, this topic would be appropriate for a NICE appraisal.	Thank you for your comment. No changes to the scope required.
Wording	Sanofi	To align with the proposed licensed indication in sections “Draft remit/evaluation objective”, “The technology” and “Population(s)”, Sanofi proposes that the population is described as “patients with newly diagnosed active multiple myeloma [redacted]”. This revision ensures that the population under consideration accurately reflects the proposed licensed	Thank you for your comment. The remit wording has been kept in line with the publicly available clinical trial information

Section	Stakeholder	Comments [sic]	Action
		indication for isatuximab (see Comment 2 below for further details).	for transparency. NICE will evaluate the technology within its marketing authorisation.
	Myeloma UK	The wording of the scope reflects the issues of clinical and cost effectiveness.	Thank you for your comment. No changes to the scope required.
Timing Issues	Sanofi	The timing of this evaluation is critical given the current landscape of multiple myeloma treatment. Multiple myeloma is a progressive, incurable cancer, with worsening outcomes at each subsequent relapse. The availability of quadruplet regimens in the front-line setting is becoming standard of care particularly for induction therapy of transplant patients. Here, isatuximab in combination with bortezomib, lenalidomide, and dexamethasone (IVRd), has been shown to improve outcomes compared with triplet regimens in IMROZ pivotal trial. This indicates a need for a first quadruplet combination therapy leading to improved outcomes in NDMM patients [redacted]. In addition, the European Medicines Agency (EMA) application his application is being reviewed under the International Recognition Procedure (IRP), which allows for a fast-tracked review by the Medicines and Healthcare products Regulatory Agency (MHRA) in the UK. Given these considerations, the evaluation of isatuximab should be prioritized and if feasible proportionate approaches considered, to ensure that patients can benefit from this promising treatment as soon as possible.	Thank you for your comment. NICE has scheduled this topic into its work programme. For further details, please see the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ta10912 No changes to the scope required.

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	Myeloma UK	Myeloma is a relapsing and remitting, incurable cancer, and even after successful treatment, it will come back. New drugs and treatment combinations are needed to extend remission times and ultimately life expectancy.	Thank you for your comment. NICE has scheduled this topic into its work programme. For further details, please see the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ta10912 No changes to the scope required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Sanofi	The background information provided in the draft scope accurately reflects the current understanding of multiple myeloma.	Thank you for your comment. No changes to the scope required.
	Myeloma UK	We consider this information to be sufficient and accurate.	Thank you for your comment. No changes to the scope required.

Section	Consultee/ Commentator	Comments [sic]	Action
Population	Sanofi	Sanofi proposes a revision to align the population description with the wording for the proposed licensed indication. Specifically, we suggest that the population is described as “patients with newly diagnosed active multiple myeloma [redacted]”.”. This ensures to align the reimbursement decision with the marketing authorization given the unmet need in this population.	Thank you for your comment. The remit wording has been kept in line with the publicly available clinical trial information for transparency. NICE will evaluate the technology within its marketing authorisation.. No changes to the scope required.
	Myeloma UK	We consider the population to be appropriately defined.	Thank you for your comment. No changes to the scope required.
Subgroups	Sanofi	No subgroups have been identified for which isatuximab in combination with bortezomib, lenalidomide and dexamethasone is expected to be more clinically effective and cost effective. Sanofi do not believe there are any other groups that should be examined separately.	Thank you for your comment. No changes to the scope required.
	Myeloma UK	We are not aware of any groups within this population that should be considered separately. The trial for this treatment combination is ongoing and trial results have not been published in a peer reviewed journal.	Thank you for your comment. No changes to the scope required.

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Comparators	Sanofi	The order of comparators in the draft scope appears to require adjustment. Specifically, bortezomib with an alkylating agent and corticosteroid is typically indicated for patients who are unable to tolerate, or have contraindications to, thalidomide. Therefore, it would be more appropriate to consider this regimen after thalidomide-based therapies in the sequence of potential comparators. Sanofi proposes the following list of potential comparators: - Thalidomide with alkylating agent and corticosteroid - Daratumumab with lenalidomide and dexamethasone For people who are unable to tolerate, or have contraindications to thalidomide: - Lenalidomide with dexamethasone - Bortezomib with alkylating agent and corticosteroid. Sanofi acknowledges that DRd (Daratumumab, Lenalidomide and dexamethasone), Rd (Lenalidomide and dexamethasone), thalidomide-based therapies, and bortezomib-based therapies have received positive NICE guidance. To accurately reflect NHS practice in England, Sanofi has utilised IQVIA market research data. The findings reveal that thalidomide-based regimens, such as MPT (Melphalan, Prednisone and Thalidomide) and CTd (Cyclophosphamide, Thalidomide and dexamethasone), are no longer employed. This was corroborated during an advisory board organised by Sanofi in November 2023. Moreover, these treatments were not considered in the recent TA917 decision-making process. As a result, Sanofi does not consider thalidomide-based regimens as relevant comparators.	Thank you for your comment. The comparators are kept broad in the scope to avoid excluding potentially relevant comparators during the appraisal. Bortezomib with alkylating agent and corticosteroid will remain in the scope as a potential comparator. The scope has been amended to remove thalidomide with alkylating agent and corticosteroid from the list of comparators.

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The use of bortezomib-based regimens, particularly VMP, has declined since the introduction of DRd. Before DRd was available, the proportion of new patients prescribed with VMP was around [redacted]. However, as of January and February 2024, VMP was only prescribed to [redacted] of new patients, while DRd was prescribed to [redacted] of new patients. This indicates a significant decrease in the use of VMP following the introduction of DRd. This suggests that VMP has been phased out as a treatment option in clinical practice, a trend expected to continue with DRd gaining more market shares by the time of the IVRd submission. According to the DRd resource impact report (TA917), it is anticipated that DRd will capture approximately 65% of the market share in 2024-2025.

Furthermore, it's important to note the projected decline in the overall proportion of patients taking VMP. As of January/February 2024, about [redacted] of all patients were on VMP. However, given the fixed duration design of VMP, this proportion is expected to decline toward 0% by the time of assessment. This further underscores the transition in clinical practice away from VMP towards other treatment options like DRd.

In light of their usage in clinical practice, DRd, Rd, and VCd only should be considered as relevant comparators. These treatments seem to correspond to [redacted] of new patients respectively. This approach ensures a more accurate and relevant appraisal of isatuximab, as it aligns the comparison with treatments currently in use within the NHS.

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<tr><th rowspan="2">Treatment</th><th rowspan="2">Guidelines</th><th rowspan="2">EMA license</th><th rowspan="2">NICE Guidance</th><th colspan="3">IQVIA market research – New patients</th><th rowspan="2">Included in TA917</th><th rowspan="2">Considered as relevant comparator</th></tr>
<tr><th>Jul/ Aug '23 (n=40)</th><th>Sep/ Oct '23 (n=37)</th><th>Jan/ Feb '24 (n=53)</th></tr>
<tr><td>DRd</td><td>Yes</td><td>Yes</td><td>Yes; TA917</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>N/A</td><td>Yes</td></tr>
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		<table><tr><td>**Rd**</td><td>Yes</td><td>Yes</td><td>Yes; TA587</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>Yes</td><td>Yes</td></tr><tr><td>**VCd**</td><td>Yes</td><td>No</td><td>Yes; TA228</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>Yes</td><td>Yes</td></tr><tr><td>**VMP**</td><td>Yes</td><td>Yes</td><td>Yes; TA228</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>Yes</td><td>No</td></tr><tr><td>**MPT**</td><td>Yes</td><td>No</td><td>Yes; TA228</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>Company included, but not part of decision-making</td><td>No</td></tr><tr><td>**CTd**</td><td>Yes</td><td>Yes</td><td>Yes; TA228</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>Company included, but not part of decision-making</td><td>No</td></tr></table> *The IQVIA study was conducted in the UK with 65 specialists, each of whom completed a short online survey about their transplant ineligible NDMM patients. Data are available for every two-month period, except for November and December 2023.*	
	Myeloma UK	We agree that the treatments listed are approved/available for use as an initial treatment for myeloma patients when a stem cell transplant isn't suitable. However, this list does not reflect the treatments patients receive in clinical practice. The main treatment used to treat this group of patients is daratumumab in combination with lenalidomide and dexamethasone. Some patients, particularly those with severely reduce kidney function, may get bortezomib in combination with cyclophosphamide and dexamethasone. A small number of patients will get lenalidomide and dexamethasone. Thalidomide based combinations are not typically used to treat this patient	Thank you for your comment. The scope has been amended to remove thalidomide with alkylating agent and corticosteroid from the list of comparators.

Section	Consultee/ Commentator	Comments [sic]	Action
		population.	
	J&J Innovative Medicine	Bortezomib with alkylating agent and corticosteroid is only available for people who are unable to tolerate, or have contraindications to thalidomide [TA228]. Thalidomide with alkylating agent and corticosteroid is incorrectly specified for people who are unable to tolerate, or have contraindications to thalidomide.	Thank you for your comment. The scope has been amended to remove thalidomide with alkylating agent and corticosteroid from the list of comparators.
Outcomes	Sanofi	Sanofi suggest adding Time to Discontinuation (TTD) to the list of outcome measures. The outcome measures to be considered include: • overall survival • progression-free survival • response rates (CR and VGPR or better) • time to discontinuation • minimal residual disease (MRD) negative status • adverse effects of treatment • health-related quality of life.	Thank you for your comment. The scope has been amended to include time to treatment discontinuation as an outcome.
	Myeloma UK	Yes	Thank you for your comment. No changes to the scope required.

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Equality	Sanofi	There is currently variability of access to treatments within the NDMM population: - At present, there is a noticeable disparity in the treatment options available to patients diagnosed with NDMM. Specifically, patients who are eligible for Autologous Stem Cell Transplant (ASCT) have access to quadruplet combination therapy as induction. However, those who are ineligible for ASCT, often due to age, frailty and/or comorbidities, or those with no intent to transplant are not afforded the same range of treatment options. The introduction of IVRd as the first quadruplet combination therapy, presents a significant opportunity to bridge this gap in improved outcomes for this important first remission. - Patients with renal impairment frequently encounter a limited range of treatment options. Historically, these patients have been treated with a bortezomib-based therapy such as VCd (Bortezomib, Cyclophosphamide, and Dexamethasone). While the DRd regimen is now available, it does not include bortezomib, which has proven effective in this patient population. The IVRd regimen uniquely combines both an anti-CD38 therapy and bortezomib, introducing an efficacious treatment option both for patient with and without renal impairment. - Patients with High Cytogenetic Risk Abnormalities (HCRA) and 1q21 amplification have demonstrated suboptimal outcomes when treated with DRd. The introduction of the IVRd has shown promising results in this high-risk subgroup. It could therefore reduce treatment outcome inequality for these patients and address a significant unmet need in the management of NDMM.	Thank you for your comment. The issues highlighted are not equalities issues because they do not relate to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. The committee will consider any potential equalities issues during the course of the appraisal.
	Myeloma UK	We don’t anticipate that a positive recommendation would impact people within the patient population for which the treatment is be licensed, who are protected by the equality legislation differently to the wider population.	Thank you for your comment. This has been added to the

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		As with all treatments the costs incurred by hospital visits and time off work will have a more significant impact on people with lower incomes.	Equality Impact Assessment form issued along with the final scope. The committee will consider any potential equalities issues during the course of the appraisal.
Questions for consultation	Sanofi	**Are thalidomide combination treatments still commonly used in NHS practice in England for multiple myeloma when stem cell transplant is unsuitable?** See Comment 2 “Comparators” section for further details. **Would bortezomib with an alkylating agent and corticosteroid or lenalidomide with dexamethasone ever be used as a first line treatment where thalidomide combination treatments could be tolerated or was not contraindicated?** According to the latest practices discussed in the section “Comparators”, thalidomide-based regimens are no longer in use for the treatment of patients NDMM who are ineligible to transplant. Therefore, the condition of intolerance or contraindication to thalidomide, which previously influenced the choice of first-line treatment, is no longer relevant. As a result, all treatments, including bortezomib with an alkylating agent and corticosteroid, as well as lenalidomide with dexamethasone, could be used as first-line treatments. However, it should be noted that all bortezomib-based regimens are not used in clinical practice anymore. See Comment 2 “Comparators” section for further details.	Thank you for your comment. Comments relating to comparators are addressed above**.** The committee will consider evidence submitted for any additional health related benefits not captured in QALY calculations during the appraisal. No further changes to the scope required.

Section	Consultee/ Commentator	Comments [sic]	Action
		Have all the relevant comparators been included in the scope? See Comment 2 “Comparators” section for further details. **Where do you consider isatuximab will fit into the existing care pathway for multiple myeloma?** Isatuximab in combination with bortezomib, lenalidomide and dexamethasone is expected to be indicated for the treatment of patients with newly diagnosed active multiple myeloma [redacted]”. This positions isatuximab as a potential first-line treatment option in the care pathway for multiple myeloma. **Would isatuximab be a candidate for managed access?** Isatuximab is expected to be available to the NHS via routine commissioning. **Do you consider that the use of isatuximab can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?** The use of isatuximab can result in potential substantial health-related benefits that are unlikely to be included in the QALY calculation. Here are some of the key benefits: - Patient and caregiver: the use of the IVRd regimen, which includes isatuximab, can potentially alleviate the symptom burden associated with multiple myeloma. This includes symptoms such as bone pain, anaemia, renal impairment and hypercalcaemia, thereby enhancing patients’ day-to-day functioning and overall well-being. By easing disease symptoms and complications, it can also lessen the physical and emotional burden on caregivers, an outcome often not measured. - Mental health: improved disease control and reduced inequality of	

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		access with the IVRd regimen can lead to reductions in anxiety and depression that are often associated with a cancer diagnosis and treatment. This improvement in mental health is a crucial aspect that is not always directly quantified in QALY assessments. - Social and economic impact: the improved health outcomes with the IVRd regimen can enable patients to maintain their employment or return to work sooner if they are within the working age. This not only contributes economically but also enhances their sense of purpose and identity. Additionally, better health can positively affect family dynamics by reducing stress and improving relationships, which are important aspects of overall well-being. These social and economic impacts are often overlooked in traditional health assessments. **Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits.** Clinicians' and patients' experiences can illustrate and highlight these aspects. **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 isatuximab 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**	

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		group to access the technology; • **could have any adverse impact on people with a particular disability or disabilities.** See Comment 2 “Equality” section for further details. **Please tell us what evidence should be obtained to enable the committee to identify and consider such impacts.** The IMROZ clinical trial and clinical practice provide the necessary evidence for the committee to consider these impacts.	
	Myeloma UK	**Would isatuximab be a candidate for managed access?** Yes – the trial is still ongoing. **Do you consider that the use of isatuximab can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?** Improving remission times and life expectancy will positively impact carers and family members. It is a treatment for newly diagnosed patients. The first remission is often the deepest, longest remission and the period when a patient's quality of life is highest. It is widely held as the best opportunity to gain the best response with the longest time until disease progression. It is also the point in their disease where many patients will have the best quality of life post-diagnosis because their burden of treatment and illness is less than patients who are multiply relapsed.	Thank you for your comment. The committee will consider evidence submitted for any additional health related benefits not captured in QALY calculations during the appraisal.

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

None