National Institute for Health and Care Excellence

Health Technology Evaluation

Isatuximab with pomalidomide and dexamethasone for treating relapsed and refractory multiple myeloma [Review of TA658] [ID4067]

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

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Comment 1: the draft remit and proposed process

Section	Stakeholder	Comments [sic]	Action
Wording	Sanofi	The wording of the remit is appropriate as it aligns with the marketing authorisation for isatuximab in combination with pomalidomide and dexamethasone. Sanofi intends to submit evidence as per the initial appraisal [TA658], supporting a 4th line only position.	Thank you for your comment. No action needed.
	Myeloma UK	Myeloma UK considers the remit to reflect the issues of clinical and cost effectiveness.	Thank you for your comment. No action needed.
Timing Issues	Sanofi	Timing of this appraisal is appropriate. Isatuximab continues to be accessible to patients whilst the review is conducted.	Thank you for your comment. No action needed.

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	Myeloma UK	No comments.	Thank you for your comment. No action needed.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Sanofi	No comments, the background is accurate and complete.	Thank you for your comment. No action needed.
	Myeloma UK	We consider this information to be sufficient and accurate.	Thank you for your comment. No action needed.
The technology/intervention	Sanofi	No comments, the description of the technology is accurate.	Thank you for your comment. No action needed.
	Myeloma UK	The description is accurate.	Thank you for your comment. No action needed.
Population	Sanofi	At the initial NICE appraisal for Isatuximab in combination with pomalidomide and dexamethasone (IsaPd), Sanofi had submitted evidence to support a 4th line only positioning and was recommended in this population within the Cancer Drugs Fund from November 2020.	Thank you for your comment. The population in the scope most closely reflects the population considered

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		The ICARIA-MM trial (pivotal phase 3 study supporting the marketing authorisation) had included patients that received a median of 3 prior lines of treatment and who had received at least 2 prior lines of therapy including lenalidomide and a proteosome inhibitor (PI). By fourth line, patients are likely to be refractory to lenalidomide and a PI and therefore, the positioning of an anti-CD38 and second-generation immunomodulatory drug combination such as IsaPd is a useful choice in clinical practice. There is long-standing evidence to also suggest that the trial comparator, pomalidomide in combination with dexamethasone (Pd), is predominantly used at this point in the pathway. The steady uptake of IsaPd in 4th line within the CDF, provides further support to this positioning and the need for IsaPd at this line of therapy. Furthermore, it is at this position where the clinical benefit of IsaPd is optimised and hence where greatest value from its use can be achieved. Considering the above, Sanofi believe that the 4th line, relapsed and refractory myeloma population remains most appropriate for the re-review of IsaPd and will provide an evidence submission which continues to support positioning IsaPd at 4th line in clinical practice.	in isatuximab's marketing authorisation. Stakeholders can provide justification around the most appropriate population and the committee will consider this during the appraisal. No action required.
	Myeloma UK	We consider the population to be appropriately defined. We welcome that it has not been restricted and is in line with the approved marketing authorisation. We note that this reflects a wider patient population than that currently approved via the Cancer Drugs Fund (CDF) and hope this signals a willingness to widen access for patients to this treatment combination. Despite approvals for treating myeloma in recent years given the heterogeneity of the disease an unmet need remains and there is a need for flexibility at each stage of the pathway.	Thank you for your comment. No action required.

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		If the company seeks to pursue NICE approval for a narrower patient population than the final marketing authorisation it is vital that this reflects unmet need, current and likely future gaps in the pathway, and is not just driven by commercial considerations.	
Comparators	Sanofi	As mentioned above, the clinical and cost effectiveness evidence Sanofi submits will be focused on comparators relevant for people who have had 3 prior therapies only (4th line): • pomalidomide plus dexamethasone (Pd) • daratumumab monotherapy Reasons for not considering other comparators to be relevant to the scope are described below. *Panobinostat plus bortezomib and dexamethasone (PanVd):* PanVd will not be included as a comparator given ongoing insight that the therapy is reserved for 5th line use due to concerns around toxicity. Subsequent therapy data from SACT demonstrate that PanVd was used after daratumumab and IsaPd and advice from clinical experts during committee meetings have led to appraisal committees routinely accepting PanVd as a 5th line therapy option. This was the case during the initial NICE appraisal of IsaPd [TA658] and more recently at the daratumumab monotherapy re-appraisal in 2021 for use at 4th line. *Ixazomib plus lenalidomide and dexamethasone (IxaRd):* IxaRd is not an appropriate comparator as the combination includes lenalidomide (R) and would be prescribed to patients that are not refractory to lenalidomide (the pivotal trial for IxaRd excluded patients that were refractory to lenalidomide). IsaPd is indicated in patients that had received at least 2 lines of therapy including lenalidomide and PI. Among this population many	Thank you for your comment. Panobinostat plus bortezomib and dexamethasone has been removed as a comparator in line with the committee's conclusion in TA658 and stakeholder comments received during consultation. Ciltacabtagene autoleucel has also been added to the list of comparators in response to consultation comments from other stakeholders. Other comparators remain unchanged at this stage. Stakeholders can provide justification around the most appropriate

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		are relapsed and refractory to lenalidomide. The patient population eligible for treatment with IxaRd is therefore fundamentally different to those considered for treatment with IsaPd. *Belantamab mafodotin and elranatamab:* The patients enrolled in the registrational clinical trials for these products are triple-class refractory (refractory to an IMiD, PI and an anti-CD38 antibody). Since IsaPd is an anti-CD38 antibody and IMiD combination, the patients eligible for treatment with IsaPd, (those not previously refractory to an anti-CD38 antibody) would not be prescribed belantamab or elrantamab. Therefore, the patient populations within the pivotal studies for these anti-myeloma therapies had to meet different eligibility criteria in this regard, and hence were a more highly relapsed/refractory population based on the median number of prior therapies (n=7 for belantamab mafodotin in the DREAMM-2 study; n=5 for elranatamab in the MagnetisMM-3 study). Given that the introduction of anti-CD38 antibody therapies at earlier lines in clinical practice is relatively recent, the majority of anti-CD38 use remains to be at 4th line (either through the availability of IsaPd in the CDF or daratumumab monotherapy). Hence belantamab and elranatamab are most likely to be used 5th line or later, subject to positive recommendation by NICE expected in June 2023 and Feb 2024 respectively.	comparators and the committee will consider this during the appraisal.
	Myeloma UK	We agree that these are the treatments available, or which will be available pending NICE review to patients who have received two or more prior lines of treatment. However, the list does not include teclistamab and cilta-cel which are being evaluated by NICE and therefore may be available to patients who have received three or more prior treatments. Myeloma UK believes that:	Thank you for your comment. Ciltacabtagene autoleucel has been added to the list of comparators. Teclistamab was not added to the list of comparators because

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		Pomalidomide plus dexamethasone, and daratumumab monotherapy should be the standard comparators. In current clinical practice it is our understanding that patients, after at least 2 prior therapies, will receive: • Ixazomib plus lenalidomide and dexamethasone (IRD use limited due to previous exposure to lenalidomide) OR • Lenalidomide and dexamethasone (RD) (use limited due to previous exposure to lenalidomide and availability of IRD) • Cyclophosphamide and dexamethasone OR alternative alkylating chemotherapy and corticosteroid (when IRD or RD is not suitable) • Clinical trial In current clinical practice it is our understanding that patients, after at least 3 prior therapies, will receive: • Pomalidomide plus low-dose dexamethasone • Daratumumab monotherapy (use limited by exposure to daratumumab at earlier lines and availability of combination treatments) • Isatuximab plus pomalidomide and dexamethasone OR • Cyclophosphamide and dexamethasone OR alternative alkylating chemotherapy and corticosteroid (when pomalidomide plus low-dose dexamethasone is not suitable) • Ixazomib plus lenalidomide and dexamethasone (use limited due availability at 3rd line)	NICE is suspending its evaluation from its current work programme. Panobinostat plus bortezomib and dexamethasone has been removed as a comparator in line with the committee's conclusion in TA658 and stakeholder comments received during consultation. Other comparators remain unchanged at this stage. Stakeholders can provide justification around the most appropriate comparators and the committee will consider this during the appraisal.

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		• Clinical trial • Compassionate use / Early access scheme However, • the combination of panobinostat plus bortezomib and dexamethasone is not widely used in clinical practice and should not be used as a comparator in this NICE appraisal. • the combination of lenalidomide and dexamethasone should not be used as a comparator in this NICE appraisal. It is not widely used at later lines due to exposure at earlier lines and prior exposure to lenalidomide is a requirement for isatuximab eligibility. • the combination of cyclophosphamide and dexamethasone OR alternative alkylating chemotherapy and corticosteroid is only used when other options (e.g PD) are not suitable and therefore should not be used as the standard comparator in this NICE appraisal. ixazomib with lenalidomide plus dexamethasone should not be used as the standard comparator in this NICE appraisal. We believe the patient cohort receiving isatuximab will differ to those receiving IRD. This is because the isatuximab combination is suitable for lenalidomide refractory patients.	
Outcomes	Sanofi	In addition to the outcomes in the draft scope, time to treatment discontinuation (TTD) will also be presented. It will be used to apply the duration of costs for the IsaPd and Pd arms. This approach was presented in the initial appraisal and was accepted by the EAG and committee.	Thank you for your comment. Time to treatment discontinuation has

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			been added to the scope as an outcome.
	Myeloma UK	Yes	Thank you for your comment. No action needed.
Economic analysis	Sanofi	Due to recent changes to the NICE methods and processes and ongoing challenges in demonstrating cost effectiveness of combination therapies such as IsaPd, where it is possible that IsaPd would not be cost-effective even if isatuximab was priced at £0, there is a need for flexibility in the re-appraisal of IsaPd. Sanofi anticipate presenting several non-reference case analyses to demonstrate the value of IsaPd. This could include but is not limited to: - Cost per PFS/OS month analysis vs comparators - Analyses considering patent expiry for pomalidomide - Applying methodology to demonstrate value attribution to constituent therapies in a combination Sanofi would also like to work collaboratively with NHSE and NICE to identify an appropriate commercial solution.	Thank you for your comment. Economic analysis methodology can be discussed further throughout the appraisal. No action required.
	Myeloma UK	No comments.	Thank you for your comment. No action needed.

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Equality	Sanofi	None identified	Thank you for your comment. No action needed.
	Myeloma UK	No comments.	Thank you for your comment. No action needed.
Other considerations	Sanofi	In September 2022, Sanofi had provided a response to the Engagement on NICE guidance updates following managed access for therapies that remained in the CDF whilst the new NICE methods and processes were introduced. Despite highlighting our concerns during the engagement, the upcoming review of IsaPd after a period of managed access is now expected to be considerably different in terms of its proposed scope and methods of assessment. Implementation of a severity modifier in place of the end-of-life criteria • Sanofi entered a MAA under the understanding that upon exit, IsaPd would be assessed at the same threshold (£50,000/QALY) and only uncertainties that remained from the previous appraisal are required to be addressed. Procedural equity concerns • Other RRMM treatments positioned at the same point in the treatment pathway as IsaPd (4th line) have until recently been reassessed under the	Thank you for your comment. The new methods including consideration of a severity modifier came into effect from 1 February 2022, as per NICE's combined methods and processes manual and topic selection manual. No action needed.

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		EOL criteria of up to £50,000/QALY. We therefore believe isatuximab has been unfairly penalised due to the relative timing of its reappraisal. • The significant changes to NICE methods during the period IsaPd was available in the CDF is likely to result in a considerable decrease in the acceptable CE threshold at a point in the disease where on average patients have less than two years left to live. Sanofi request that the appraisal committee and all other relevant stakeholders are made aware of the revised terms followed for this reappraisal compared to the pre- 2022 CDF review process. We also urge the appraisal committee and relevant stakeholders to consider applying flexibility in the re-assessment of IsaPd, given that the changes to NICE methods and processes discussed above, and the unresolved issue of demonstrating cost-effectiveness of branded combination therapies are likely to result in a significantly challenging reappraisal for IsaPd.	
	Myeloma UK	No additional suggestions	Thank you for your comment. No action needed.
Innovation	Sanofi	IsaPd was designated a promising innovative medicine (PIM) status by the MHRA in 2019 and has demonstrated substantial PFS gains compared to current baseline commissioned treatments at 4th line. This supports the ongoing need for varied, safe and efficacious treatments with synergistic modes of action such as IsaPd, in the relapsed and refractory population.	Thank you for your comment. No action needed.

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	Myeloma UK	Yes, we would consider this an innovative treatment option for relapsed and/or refractory myeloma patients. Monoclonal antibodies are relatively new and highly effective treatments for myeloma. Myeloma remains incurable and even after successful treatment, almost all patients eventually become resistant to existing treatments. New drugs and treatment combinations are urgently needed to overcome treatment resistance. Myeloma is a heterogenous cancer comprised of several difference subclones. Therefore, combination treatments with complimentary mechanisms of action, where available, are preferred. This combination gives patients with limited options and potentially poor outcomes access to an anti-CD38 monoclonal antibody containing triplet. In particular, the absence of lenalidomide in this triplet combination is a significant patient benefit. There is an increase in lenalidomide refractory patients at 3rd and 4th line following the approval of lenalidomide maintenance and its increased use earlier in the pathway.	Thank you for your comment. No action needed.