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| •  Dr Mark Chakravarty  Lead Non-executive Director NICE Appeals  National Institute for Health and Care Excellence  2nd Floor  2 Redman Place  London E20 1JQ  • |
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4th July 2024

Dear Dr Chakravarty,

**APPEAL AGAINST THE FINAL DRAFT GUIDANCE FOR** **ISATUXIMAB WITH POMALIDOMIDE AND DEXAMETHASONE FOR TREATING RELAPSED AND REFRACTORY MULTIPLE MYELOMA [ID4067]**

**EXECUTIVE SUMMARY**

Sanofi brings this appeal in order to address serious procedural issues arising in this appraisal and to the reasonableness of the Appraisal Committee’s conclusions following its assessment of isatuximab with pomalidomide and dexamethasone for the treatment of relapsed and refractory multiple myeloma. Sanofi is particularly concerned that the appraisal of isatuximab has not adequately taken into account the particular difficulties associated with the assessment of combination treatments and has not incorporated the flexible approach required in view of the change in methodology adopted by NICE between Cancer Drugs Fund (CDF) entry and review including the different cost-effectiveness standard applied to components of combination treatment including isatuximab as well as comparator technologies. Our points of appeal are as follows:

Ground 1

* 1. There is no indication that the Appraisal Committee understood that applying NICE’s standard methodology means that isatuximab cannot be cost effective even at zero price
  2. NICE and the Appraisal Committee have not explained how, if at all, they have taken into account the fact that elements of the combination and comparators were appraised under NICE’s previous methodology, subject to a higher ICER threshold
  3. NICE’s proposed discontinuation of the appraisal rather than consideration of a flexible approach to its standard methodology was unfair
  4. NICE’s refusal to refer isatuximab for commercial negotiation was inadequately explained and deprived Sanofi of the possibility to reach a satisfactory outcome to this appraisal
  5. The Appraisal Committee failed adequately to consider the non-reference case analyses submitted by Sanofi
  6. The Appraisal Committee’s conclusion that it is unable to base its decision on removing the costs of pomalidomide and dexamethasone, because NICE recommends these products as cost effective misinterprets the Manual and improperly fetters its own discretion

Ground 2

2.1 The Appraisal Committee’s conclusion that a standard reference case analysis should be used for decision making disregards the particular circumstances of this appraisal and results in an outcome that is perverse

2.2 The inconsistent approach to modelling effectiveness of daratumumab is unreasonable

2.3 The Committee’s approach to comparing the efficacy of isatuximab in combination with pomalidomide and dexamethasone does not reflect the evidence available and is therefore unreasonable

2.4 The Committee’s conclusion that the early survival benefit for isatuximab in combination demonstrated in the SACT datasets is not plausible disregards consistent evidence from the ICARIA-MM trial and is therefore unreasonable

2.5 The inconsistent approach to assessment of utilities adopted in this appraisal relative to TA658 is unreasonable based on the evidence available

**INTRODUCTION**

We provide below background information in relation to relapsed and refractory multiple myeloma and isatuximab in order to assist the Appeal Panel. This summary is not intended to replace the more detailed information provided by Sanofi in its original submission on 2 March 2020 for the purposes of TA 658 or the additional data submitted for this review [ID4067] on 17 April 2023.

**Relapsed and refractory multiple myeloma**

Multiple myeloma is a malignant, progressive and incurable haematopoietic tumour of plasma cells. It is an orphan disease with an incidence of approximately 9.3/100,000 population in England; 80% of patients are aged 60 years or greater, however the majority are under 75 years old.

Affected patients report a high symptom burden and there is a substantial impact on quality of life for patients and families/ carers. Patients experience cycles of remission and relapse, with decreasing treatment response after each relapse. They receive an average of 4 to 8 different treatment regimens during their remaining lifespan, however they eventually become refractory to these therapies and further treatment options are needed. Patients with relapsed and refractory multiple myeloma, who are eligible for combination treatment including isatuximab have a life expectancy (median overall survival [OS]) of between 7.9 and 15.2 months).

**Isatuximab**

Isatuximab is an IgG1-derived humanised monoclonal antibody, which binds to a specific cell surface glycoprotein that is highly expressed on myeloma cells and triggers death of tumour cells via multiple modes of action.

It was granted a marketing authorisation by the European Commission under the centralised procedure on 30 May 2020. This was automatically converted to a Great Britain (GB) marketing authorisation on 1 January 2021.

Following initial appraisal by NICE, isatuximab was recommended in combination with pomalidomide and dexamethasone, through managed access via the CDF, for the treatment of adult patients with relapsed and refractory multiple myeloma who have received 3 prior lines of treatment (including lenalidomide and a proteasome inhibitor and have demonstrated disease progression on the last therapy (TA658), Since that time, isatuximab in combination with pomalidomide and dexamethasone has become standard of care for such patients and around 1700 patients in England have been initiated on treatment with this combination since it has been available on the CDF.

Evidence for the effects of isatuximab plus pomalidomide and dexamethasone in patients with relapsed and refractory multiple myeloma, who have had 3 previous lines of therapy is provided by the ICARIA-MM clinical trial. Median progression-free survival (PFS) in the isatuximab plus pomalidomide and dexamethasone arm of ICARIA-MM was 12.4 months, and 6.5 months in the pomalidomide plus dexamethasone arm (hazard ratio [HR] 0.536, 95% confidence interval [CI] 0.343 to 0.840). While ICARIA-MM was not powered to detect differences in overall survival (OS), a secondary endpoint, median OS has been achieved in both arms. Median OS was 33.3 months in the isatuximab plus pomalidomide and dexamethasone arm and 17.7 months in the pomalidomide plus dexamethasone arm (HR 0.657, 95% CI 0.409 to 1.055).

**PROCEDURAL HISTORY OF THE APPRAISAL**

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| **Date** | **Event** |
| 30 May 2020 | Isatuximab was granted a marketing authorization by the European Commission under the EU centralized procedure. (This resulted in the automatic grant of a Great Britain (GB) authorization on 1 January 2021, at the end of the transition period, following the withdrawal of the UK from the EU.) |
| 18 November 2020 | Publication of TA658: Isatuximab recommended for use within the Cancer Drugs Fund |
| 30 January 2023 | Decision problem meeting for Review of TA658 [ID4067] |
| 3 February 2023 | Invitation to participate in review |
| 3 February 2023 | Final scope |
| 17 April 2023 | Company submission by Sanofi |
| 10 October 2023 | EAG clarification questions sent to Sanofi |
| 24 October 2023 | Sanofi’s response to clarification questions submitted |
| 18 December 2023 | Assessment Report (Review) prepared by Sheffield Centre for Health and Related Research (SCHARR) |
| 17 January 2024 | Appraisal Committee Meeting 1 |
| 9 February – 1 March 2024 | Consultation on draft guidance |
| 14 March 2024 | Appraisal Committee Meeting 2 |
| 25 March 2024 | NICE proposes that isatuximab in combination should be referred to NHS England for commercial negotiations |
| 2 April 2024 | Sanofi agrees that isatuximab in combination should be referred to NHS England for commercial negotiations |
| 25 April 2024 | NICE advises Sanofi during telephone discussion that isatuximab in combination will not be referred for commercial negotiations |
| 13 June 2024 | Final Draft Guidance issued to stakeholders (delayed from 9 May 2024) |
| 4 July 2024 | Submission of appeal |

**GROUNDS OF APPEAL**

1. **GROUND 1a: IN MAKING THE ASSESSMENT THAT PRECEDED THE RECOMMENDATION, NICE HAS FAILED TO ACT FAIRLY**

**1a.1**  **There is no indication that the Appraisal Committee understood that, applying NICE’s standard methodology, means that isatuximab cannot be cost effective even at zero price**

It is now well established that it may be impossible, using NICE’s current standard procedure, to demonstrate cost-effectiveness of a new technology which forms part of combination treatment. The reason for this is that, whereas components of the combination and the comparator were recommended for NHS use and priced at the upper end of the acceptable range, any extension to life resulting from the new combination is likely to include continued treatment with the elements already recommended by NICE at high cost. While the price for these products was cost effective when considered under the original indication, the prolonged use associated with extended life expectancy on combination treatment is unlikely to be cost effective. This position has been made materially more challenging as a result of a change in NICE’s methodology in 2022, which removed the end of life criteria from assessment of new technologies, reduced the effective QALY weighting for conditions such as that considered in this appraisal from around 1.7 to 1.2 and reduced the effective ICER threshold for end of life treatments from £50,000 to around £30,000. The ~~substantial~~ reduction in the level of the QALY weighting has been the subject of substantial concern and will be reviewed by NICE in 2024/2025, however the particular challenges resulting from situations where combination treatments are assessed at ICER thresholds of £30,000/QALY, but components were assessed at ICER thresholds of £50,000/QALY has not been addressed.

In the above circumstances, it is incumbent on NICE to adopt an approach to appraisal despite the change in its own methodology, which is procedurally fair and avoids the perverse situation where highly effective combination therapies are excluded in favour of older regimens, simply due to the increased life expectancy following use of such combinations and/or to a change in NICE’s methodologies and the associated ICER thresholds. NICE has recognised this in certain past appraisals of combination therapies, where it has adopted a flexible approach (e.g. pertuzumab with trastuzumab and docetaxel for treating HER2-positive breast cancer (TA 509)). However the circumstances in which NICE is willing to recognise that its standard procedure is not appropriate and therefore to apply a more pragmatic approach to appraisal is not transparent with resulting inconsistency.

The difficulties arising where a new technology will not be viewed as cost-effective by NICE even at zero cost, were reviewed by ScHARR (the Assessment Group in this appraisal) acting as NICE’s Decision Support Unit in 2014[[1]](#footnote-2). The current situation is however even more difficult than that considered by ScHARR in 2014, in view of the major contribution played by the introduction of NICE’s new procedures in 2022, as described above.

Isatuximab in combination with previous standard treatment with pomalidomide and dexamethasone for the treatment of relapsed and refractory multiple myeloma was initially appraised in 2019 /2020 under NICE’s previous methodology and recommended for use via the CDF. The appraisal of the combination was challenging as pomalidomide and dexamethasone had been recommended at a price consistent with the end of life criteria and an ICER threshold of £50,000 (TA427) and a very substantial discount on isatuximab was required in order to achieve a positive outcome for the combination. Sanofi was aware that isatuximab would be assessed on CDF exit in accordance with NICE’s methodology in effect at that time, but entered into the managed access agreement in good faith. However, the challenges were substantially increased on CDF exit as a result of a change in NICE methodology effective from February 2022, which Sanofi could not have anticipated.

Sanofi therefore reminded NICE of the difficulties associated with reappraisal of isatuximab in its submission dated 17 April 2023 following CDF exit (pages 15, 16), including the probability that isatuximab would not be viewed as cost effective even if priced at zero. In that submission, Sanofi asked “NICE and the appraisal committee to take a pragmatic approach and exert flexibility in their decision making…” in the context of the review.

Clinical trial data for isatuximab as part of fourth line combination treatment for relapsed and refractory multiple myeloma are very positive and these results are reinforced by real world evidence from SACT. As a consequence, isatuximab plus pomalidomide and dexamethasone is now standard care for such patients. However NICE’s methods and, in particular, the change in the methodology with inconsistent standards applied to components of the combination and to comparators creates an unfair obstruction to baseline commissioning. Nevertheless, there is no indication in the FDG that the Appraisal Committee understood that the change in its current standard methodology contributes to the fact that isatuximab combination treatment will not be cost effective even at zero price or placed itself in a position to consider a more flexible approach to appraisal in that context.

At paragraph 3.17 of the FDG, the Appraisal Committee states:

“The company suggested that there was a need for flexibility when appraising isatuximab plus pomalidomide and dexamethasone. It said that challenges in demonstrating the cost effectiveness of combination treatments meant isatuximab plus pomalidomide and dexamethasone was unlikely to be cost effective even if it [i.e. isatuximab] was offered for free”.

However, the FDG does not state whether the Committee understood and agreed with the view expressed by Sanofi or if not, its reasons for disagreement.

While the NICE team recognised that isatuximab plus pomalidomide and dexamethasone would not be cost effective even if isatuximab were provided at zero price and communicated this to Sanofi at a meeting on 28 March 2024, this is not stated in the FDG. Therefore, while slide 27 of the public committee slides at ACM2 referred to Sanofi’s view that “highly likely it will not be cost-effective even if ISA has zero cost - a strong case to apply flexibility”, there is no indication that the Committee accepted this view and, if so, how it proposed to address the situation. Significantly the “Key issues for decision making” at slide 32 of the public committee slides do not even mention this issue.

It is Sanofi’s position that the appraisal of isatuximab is particularly complex given the fact of combination treatment and the change in NICE’s methods which mean that comparators were assessed using a different approach and at a higher ICER threshold than that available under NICE’s current methods. In these circumstances it is clearly essential that the Appraisal Committee understands the particular challenges and places itself in a position to consider how these may be addressed as a matter of fairness. There is no indication that this occurred in this case.

**1a.2 NICE and the Appraisal Committee have not explained how, if at all, they have taken into account the fact that elements of the combination and comparators were appraised under NICE’s previous methodology, subject to a higher ICER threshold**

This appraisal considers isatuximab in combination with pomalidomide and dexamethasone, which is also the principal comparator. As explained above, pomalidomide and dexamethasone were recommended by NICE in 2017 following an appraisal under the old methodology. Even allowing for the substantial benefits achieved following the addition of isatuximab, it is in practice impossible for the current combination therapy to demonstrate cost effectiveness at an ICER threshold of £30,000 in circumstances where the prices for components were agreed in accordance with an ICER threshold of £50,000.

The fact that components of isatuximab combination therapy were recommended under NICE’s previous methodology is an important factor which must be taken into account by NICE and the Appraisal Committee when considering the current appraisal. Failure appropriately to reflect this situation in decision-making creates an unequal starting point for assessment of isatuximab, favouring older treatment or monotherapy regimens and discouraging innovation. This is to the detriment of patients and contrary to standards of procedural fairness. However the FDG does not address this inequality of treatment or how it should be addressed in decision-making and there is no indication that it was taken into account by the Committee.

**1a.3 NICE’s proposed discontinuation of the appraisal rather than consideration of a flexible approach to its standard methodology was unfair**

Chapter 3 of the 2019 Voluntary Scheme for Branded Medicines Pricing and Access (VPAS) in effect at the time of initial appraisal of isatuximab and also when the review following CDF exit was commenced, included a commitment to appraisal of all new active substances (see also paragraph 4.1.4 of NICE’s Health Technology Evaluation Topic Selection Manual): In circumstances where NICE is required to conduct an appraisal, it is implicit that its procedures should be fair and appropriate. If, for some reason, NICE’s standard procedures produce an unfair or perverse result when applied to a particular technology, it is incumbent on NICE to adopt a flexible approach to ensure fairness and so that the outcome of its appraisals are appropriate for patient care and useful to the NHS. Rigid adherence to an inappropriate procedure may be the easy course but it achieves no useful outcome. This has been recognised by NICE is previous appraisals (e.g. pertuzumab with trastuzumab and docetaxel for treating HER2-positive breast cancer TA509, where the Appraisal Committee recognised the presence of exceptional circumstances in view of the fact that pertuzumab had been available for some time via the CDF.)

The particular challenges following application of NICE’s new methodology to technologies exiting managed access was discussed at a meeting of the Patient Access to Medicines Partnership (PAMP) on 1 March 2024 attended by Dr Sam Roberts and Helen Knight from NICE. At that meeting, NICE confirmed that it would proactively engage with stakeholders where it has identified that methods and process changes may impact ongoing managed access agreements and consider reasonable company requests for adjustments to the guidance update process where appropriate.

On 25 July 2023 the NICE team advised Sanofi, during a telephone call, that the appraisal of isatuximab in combination should be terminated or Sanofi should withdraw its submission. This advice was seemingly based on advice from the EAG that there was no possibility of isatuxamab being viewed as cost effective if appraised using NICE’s standard methodology. Importantly, the potential incorporation of flexibility into NICE’s standard procedures as a result of the particular circumstances of this case did not seem to be considered. While Sanofi indicated that the appraisal should continue, in the interests of patients, NICE maintained that no modification of NICE’s standard methodology would be considered and this has remained its position.

In summary, while NICE recognised that isatuximab combination treatment could not be cost effective when assessed under NICE’s standard methodology, the only option offered to Sanofi was discontinuation of the appraisal and NICE refused to consider any flexibility. The exceptional circumstances of this appraisal (similar to that with pertuzumab) did not appear to be taken into account in any way. Sanofi was simply advised to bring the matter before the appeal panel. It is Sanofi’s firm view that the overall approach followed in this appraisal is inconsistent with a fair procedure.

**1a.4 NICE’s refusal to refer isatuximab for commercial negotiation was inadequately explained and deprived Sanofi of the possibility to reach a satisfactory outcome to this appraisal**

Section 5.9 of NICE’s Manual addresses the arrangements for patient access schemes (PAS) and commercial agreements. NICE may refer a technology to NHS England for negotiation of a commercial agreement in cases where the technology is unlikely to be cost effective when considered in the context of a PAS.

Paragraph 5.9.35 states:

“If the topic is identified as high risk of not being cost effective with a simple or complex PAS alone, NICE's commercial liaison team will seek formal confirmation from NHS England and NHS Improvement that they would be willing to discuss a commercial access agreement after the committee meeting if necessary”.

The referral of isatuximab in combination to NHS England for negotiation of a commercial agreement was raised by NICE on 25 March 2024 and agreed by Sanofi on 2 April 2024. NHS England was also willing to participate in such negotiations. Sanofi was advised that NICE would prepare a commercial briefing for these purposes. However on 25 April 2024, Sanofi was advised by NICE that isatuximab would not be referred to NHS England for the purposes of commercial negotiations and instead the appraisal would proceed directly to FDG. While no adequate explanation of NICE’s consideration of this issue was provided to Sanofi and Sanofi was given no opportunity to object or make submissions, we understand that the change in approach resulted from NICE’s conclusion that no commercial agreement could result in a cost-effective outcome.

Importantly, in November 2023 the Competition and Markets Authority issued guidance on the circumstances in which manufacturers of components of combination treatments could negotiate prices for the combination with a view to achieving a cost-effective outcome. XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX. A letter from NICE to Sanofi dated 13 March 2024 in response to Sanofi’s concerns regarding the approach to this appraisal in the context of challenges demonstrating cost effectiveness for combination therapies, exacerbated by the introduction of NICE’s new methodology, indicated that Sanofi should explore a “commercial solution” as set out in the CMA framework “first”. XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX.

NICE’s decision not to refer isatuxumab in combination for commercial negotiation with NHS England conflicted with NICE’s procedures and was made despite objections by Sanofi. The decision was explained solely on a conclusion that isatuximab in combination was not cost effective even at zero price, when assessed in accordance with the Committee’s preferred assumptions. It appeared to disregard the new guidance from CMA regarding negotiation of prices for combination therapies and permitted no opportunity for considered submissions by Sanofi.

**1a.5 The Appraisal Committee failed adequately to consider the non-reference case analyses submitted by Sanofi**

At paragraph 3.17 of the FDG, the Appraisal Committee considers three non-reference case analyses submitted by Sanofi with a view to addressing the challenges resulting from the fact that isatuximab was not cost effective even if supplied at zero price, if assessed under NICE’s standard methods. The Committee dismissed each of these analyses as a basis for decision making for the reasons set out below.

* Removing pomalidomide and dexamethasone costs from the combination therapy arm.

The Committee stated simply that as pomalidomide and dexamethasone had been found to be cost effective, decision-making should be based on the reference case. The FDG makes no reference to the fact that pomalidomide and dexamethasone had been found to be cost effective under NICE’s old methodology and a different ICER threshold (£50,000/QALY) or the potential implications of this. While it is Sanofi’s case that the reason given by the Committee was incorrect and procedurally unfair (see appeal point 1a.6 below). The fact that pomalidomide and dexamethasone had previously been found to be cost effective under a different methodology did not mean that the Committee was bound to conclude that decision making should be based on the reference case. The Committee provided no explanation for this conclusion and gave no substantive consideration to the analysis submitted by Sanofi which removed the associated costs from consideration as part of combination therapy; this represents a procedural flaw in the appraisal.

* Considering potential generic pomalidomide prices because of the patent expiry expected later in 2024

The Committee concluded that there was uncertainty regarding when generic pomalidomide would become available and that, in any event, introducing generic pomalidomide would not result in cost effectiveness estimates that would fall within the range that NICE would consider acceptable. The FDG includes no assessment of how the availability of generic pomalidomide might affect the ICER for the combination even if, on its own this would not achieve cost effectiveness .

NICE also refused to apply flexibility in timings, in the form, for example, of a short delay in the appraisal to allow for the introduction of a generic version of pomalidomide. This is despite the fact that NHS England to advised NICE that a generic version would indeed appear in short order and such delays have been introduced in previous appraisals (e.g. . Ixazomib with lenalidomide and dexamethasone for treating relapsed or refractory multiple myeloma (TA870).)

* Attributing value to each of the treatments in the isatuximab plus pomalidomide and dexamethasone combination.

The Appraisal Committee made no attempt to consider value attribution but stated only that it was unable to consider such an approach without a framework..

The use of a value attribution method to address the difficulties associated with appraisal of combination therapies was raised by Sanofi in correspondence with NICE on 1 March 2024. NICE’s response dated 13 March 2024 stated:

“Finally, NICE understands that value attribution methods can be used to assess how components of a combination therapy contribute to its overall effectiveness. However, it is not the role of the appraisal committee to provide a view on this - there are no NICE methods to address this”.

The response of both NICE and the Appraisal Committee in this context is unfair and unacceptable. They did not conclude that such a solution was inappropriate (still less provide any reasons for such a conclusion), but simply stated that they did not know how to approach such analyses. If NICE currently has no framework for consideration of value attribution methods, the only fair response is to seek appropriate advice on use of such methods either from NICE’s Decision Support Unit or from the EAG. No attempt was made to do either of these things in the context of the current appraisal.

**1a.6 The Appraisal Committee’s conclusion that it is unable to base its decision on removing the costs of pomalidomide and dexamethasone, because NICE recommends these products as cost effective misinterprets the Manual and improperly fetters its own discretion**

At paragraph 3.17 of the FDG, the Appraisal Committee states:

“The committee recalled that section 4.4.16 of NICE’s health technology evaluations manual states that the committee may consider a non-reference-case analysis with the background care costs removed if the NHS is currently providing care that is expensive or would not be considered cost effective. The committee agreed that it could consider this analysis alongside the reference case analysis for context in line with the methods manual. But, it could not make its decision based solely on removing the costs of pomalidomide and dexamethasone. This was because NICE recommends pomalidomide plus dexamethasone and considers it to be cost effective”.

Section 4.4.16 of NICE’s Manual provides:

“In cases where a technology increases survival in people for whom the NHS is currently providing care that is expensive or would not be considered cost effective at NICE's normal levels, the committee may consider alongside the reference-case analysis a non-reference-case analysis with the background care costs removed. The committee will consider in its decision making both the reference-case and non-reference-case analyses, taking into account the nature of the specific circumstances of the evaluation including the population, care pathway and technology, as well as:

* the extent to which the cost effectiveness of the technology is driven by factors outside its direct costs and benefits
* if the NHS is already providing care that would not be considered cost effective at NICE's normal levels
* if the high-cost care is separate from direct, intrinsic consequences of the technology (such as a side effect or administration cost)
* the extent to which commercial solutions would address the issue”.

The meaning of “expensive” or “not cost effective” is not defined in the Manual. For the purposes of the current appraisal:

1. the Appraisal Committee has not addressed the “expensive” aspect of section 4.4.16 of the Manual. In Sanofi’s view this is an omission, which means that the Committee has not given adequate consideration to the non-reference case analysis.
2. In addition, while the Appraisal Committee has not explained its interpretation of “cost effective at NICE's normal levels”, it seems as if this requirement is construed as being met where NICE has previously issued a positive recommendation for use of a technology, even if such recommendation was issued under a previous methodology and applying a different ICER threshold from that currently applicable. Sanofi does not suggest that TA427 is no longer valid, however it is our firm view that “cost effective at NICE’s normal levels” must mean cost effective in accordance with the methodology applied by NICE at the present time, rather than any historic assessment.

In summary, the Appraisal Committee’s conclusion at paragraph 3.17 of the FDG that it was unable to rely on the non-reference case analyses and “it could not make its decision based solely on removing the costs of pomalidomide and dexamethasone”, does not reflect the wording of the Manual and constitutes an improper fetter of the Committee’s discretion in the context of this appraisal.

1. **GROUND 2: THE RECOMMENDATION IS UNREASONABLE IN THE LIGHT OF THE EVIDENCE SUBMITTED TO NICE**

**2.1 The Appraisal Committee’s conclusion that a standard reference case analysis should be used for decision making disregards the particular circumstances of this appraisal and results in an outcome that is perverse**

The challenges associated with appraisal of new combination treatments (as described under appeal points 1a.1 above) are well known to NICE and the particular difficulties resulting from NICE’s introduction of new methodologies in 2022 in circumstances where components of the combination were appraised under the old methods, are obvious. Throughout this reappraisal, Sanofi has drawn these issues to NICE’s attention including the resulting fact that the combination cannot be cost effective even at zero price and has reminded NICE of the need to consider a flexible and pragmatic approach (such as that adopted in TA509 referenced above) in order to avoid an irrational outcome.

Despite the submissions by Sanofi however, at paragraph 3.17 of the FDG, the Appraisal Committee states:

“But having taken into account the specific circumstances of this evaluation, that is, that pomalidomide and dexamethasone has been assessed to be cost effective, it maintained its view that the reference case analysis should be used for decision making”.

In view of the complexities arising from the inclusion of isatuximab as part of combination treatment together with components (pomalidomide and dexamethasone) recommended by NICE and priced to meet the upper end of the applicable ICER threshold, demonstration of cost effectiveness, even at zero price, appears to be impossible. This situation has been accepted by NICE. The position is even more difficult, given the change in NICE’s methodologies in 2022 which mean that an ICER threshold of £50,000 was applicable to pomalidomide and dexamethasone in 2017, but a threshold of £30,000 (dependent on QALY weighting) is applicable to the isatuximab combination in 2024. The result of the situation and the associated inequality, is that, while the data from the ICARIA-MM trial demonstrate substantial benefits in terms of PFS and OS associated with the combination treatment versus standard therapy it is impossible to demonstrate cost effectiveness for the combination in view of the pricing of the pomalidomide and dexamethasone components previously approved by NICE, under its previous methodology. Unless some flexibility of approach is introduced, patients will be deprived access to the superior benefits of the triplet combination as a result of NICE’s previous recommendation of the price for the two components which also comprise current standard therapy for fourth line treatment of relapsed and refractory multiple myeloma.

This outcome is irrational. The use of health economic modelling should be viewed as a tool to guide decision making, not the end in itself. Where, as here, the standard methodology results in perverse consequences (particularly where inconsistent procedures have been applied with resulting inequality) a reasonable approach requires introduction of pragmatism to achieve an outcome in the interests of patients and the NHS. Such an approach has been applied in other appraisals and should reasonably be followed here.

**2.2 The inconsistent approach to modelling effectiveness of daratumumab is unreasonable**

As a general principle, NICE is committed to consistency in approach both as a matter of procedural fairness and so that appropriate comparisons can be made between different appraisals. Any inconsistency must therefore be appropriately justified, failing which the decision making is arbitrary and unreasonable.

In the current appraisal the EAG has selected a different approach to modelling OS for daratumumab using SACT data to that relied upon in TA783. The Committee has accepted the EAG’s approach. The EAG’s reasons are set out at paragraph 3.11 of the FDG:

“The EAG explained that in TA783 daratumumab was being appraised, so it was reasonable to use a conservative distribution [Weibull] because there was a risk of recommending a treatment that was not cost effective. It considered that in this appraisal, where daratumumab is a comparator, the best fitting distribution should be used. So the EAG selected the RCS log-normal 2-knot distribution. The committee agreed with the EAG’s comments. It noted that the RCS log-normal 2-knot distribution was not considered by the company or EAG in TA783. It also noted that in TA783 the EAG and company agreed on the choice of distribution to extrapolate OS, so it was not one of the specific issues considered by the committee. The committee also noted that the company’s approach appeared to underestimate the tail end of the Kaplan–Meier curve from the SACT data”.

NICE’s procedures do not suggest that inconsistency is acceptable depending on whether a technology under appraisal or a comparator is being considered and the aim of NICE appraisals is to achieve a fair and balanced assessment of evidence rather than to create an inequality between the technology and its comparators. In these circumstances it is unreasonable to select one modelling approach for the purposes of one appraisal and another in the context of another appraisal simply because the results are more or less favourable. The fact that the EAG and the company agreed that a Weibull approach was appropriate in TA783 is consistent with the fact that it represented a fair and balanced modelling method. No new evidence has emerged since TA783 to justify a change in modelling approach and the new method proposed by the EAG is arbitrary.

**2.3 The Committee’s approach to comparing the efficacy of isatuximab in combination with pomalidomide and dexamethasone does not reflect the evidence available and is therefore unreasonable**

The data from ICARIA-MM were confounded by post study treatments including therapies that are not used within the NHS. For this reason, Sanofi believed that any use of the ICARIA-MM data to compare the efficacy of isatuximab in combination compared with pomalidomide and dexamethasone would be unreliable and therefore submitted a naïve comparison of datasets from the SACT database for the purposes of the current appraisal, reflecting real world evidence in a UK setting. The Committee expressed concern that the naïve comparison might not account for confounding factors (although, where data were available, patient characteristics were similar between groups) and one of the clinical experts suggested that the SACT data under estimated survival for patients treated with pomalidomide and dexamethasone. Based on this assessment the Committee concluded at paragraph 3.5 of the FDG:

“…the naïve comparison was likely to overestimate the relative treatment effect of isatuximab plus pomalidomide and dexamethasone and that the data from ICARIA-MM provided a more robust estimate of relative effect”.

However, there is no evidence that patient characteristics were different between datasets and, while the EAG suggested that patients who received isatuximab in combination might have been fitter than patients who received pomalidomide and dexamethasone and that exclusion of patients who may have received pomalidomide and dexamethasone after receiving a treatment available on the CDF might have excluded the fittest patients, this was refuted by Myeloma UK.

Based on this conclusion, the Committee rejected the naïve comparison of datasets from SACT and stated that it preferred to rely on a simulated pomalidomide and dexamethasone extrapolation using the unadjusted hazard ratio from ICARIA-MM and the isatuximab combination SACT data. In reaching this conclusion, the Committee:

* Relied substantially on the opinion of one of the clinical experts that the SACT data for pomalidomide and dexamethasone were less favourable than those seen in clinical practice, over the real world evidence from SACT;
* Disregarded the fact that the Committee’s criticism of the Kaplan-Meier curves in the SACT data at paragraph 3.5 of the FDG was addressed by data from ICARIA-MM as explained in Sanofi’s response to the Draft Guidance (see appeal point 2.4 below
* Could not adequately account for the use of post study treatments in the ICARIA-MM trial, with the result that the comparison was inevitably biased;
* Failed adequately to consider an analysis requested by the EAG and submitted by Sanofi, which used time-varying hazards to make a simulated pomalidomide and dexamethasone comparison which produced results similar to those obtained from the naïve comparison of SACT data, but said simply and without explanation that this underestimated survival for pomalidomide plus dexamethasone.

In summary therefore, the modelling approach preferred by the Committee does not represent a balanced assessment of the available evidence and is unreasonable.

**2.4 The Committee’s conclusion that the early survival benefit for isatuximab in combination demonstrated in the SACT datasets is not plausible disregards consistent evidence from the ICARIA-MM trial and is therefore unreasonable**

At paragraph 3.5 of the FDG, the Committee stated:

“It noted that the separation of the Kaplan-Meier curves in the SACT data suggested a survival benefit for isatuximab plus pomalidomide and dexamethasone within 2 months which it considered implausible”

This conclusion however did not take into account the fact that, as explained in Sanofi’s response to consultation on the Draft Guidance, data from ICARIA-MM demonstrated the same trend within the OS data for isatuximab in combination versus pomalidomide and dexamethasone in the fourth line population.

The results observed in both the SACT datasets and the ICARIA-MM trial is also scientifically plausible. Although early OS events occurred in both arms of ICARIA-MM, they were more pronounced in the pomalidomide and dexamethasone arm. This was driven to at least some extent by outcomes in patients with less than a partial response (32 of 58 patients in the pomalidomide and dexamethasone arm) for whom median OS in the trial was lower (14.13 months (95% CI: 5.815 ; 18.136) than for those with very good partial response or better (25.94 months (95% CI: 10.086 ; NC), n=7).

In the context of the consistent early benefit seen in both the ICARIA-MM clinical trial and the real world evidence from SACT, explained on the basis of response to treatment, the Committee’s conclusion at paragraph 3.5 of the FDG that this benefit is “implausible” is unreasonable.

**2.5 The inconsistent approach to assessment of utilities adopted in this appraisal relative to TA658 is unreasonable based on the evidence available**

In TA658 the Appraisal Committee accepted health related quality of life data collected from the ICARIA-MM trial using the EQ5D tool preferred by NICE, giving utility values of 0.719 for the isatuximab combination arm and 0.717 for the pomalidomide and dexamethasone arm. At that time, the Appraisal Committee accepted that it was plausible that different therapies could be associated with different utility values.

Exactly the same approach was used by Sanofi in its submission in the current appraisal, following latest NICE guidance on mapping of utility values. However, following managed access, the differences between the two groups were larger. Nevertheless, the Appraisal Committee has concluded in the FDG that the same utility values should be applied to all therapies. Paragraph 3.12 of the FDG states:

“…the committee was not convinced that people who are progression-free and on isatuximab plus pomalidomide and dexamethasone would have a higher utility than people on pomalidomide and dexamethasone who are progression free”.

The Committee’s reasons comprised:

* “….it was not convinced that a complete response would lead to better control of symptoms”.

However, the evidence of patient experts (noted at paragraph 3.12 of the FDG) was that a deeper response could have a positive psychological impact and that cyclical anxiety linked to testing, may not be captured in the clinical trial data. The Committee has provided no explanation for rejecting this evidence.

* “…it considered that there were other factors that may lead to negative utility with isatuximab”

The examples given by the Committee were adverse effects of triple therapy and the need to attend hospital for isatuximab infusions. However, there was no difference in discontinuations due to adverse events between the two arms of the ICARIA-MM trial and the Committee observations in this respect appear to be wholly speculative. Furthermore, the evidence of the patient groups was that the priority for patients is efficacy and that the requirement for intravenous infusions is acceptable if this increases efficacy and life expectancy.

Overall therefore, the Committee’s reasons for adopting an inconsistent approach to the assessment of utilities in the current appraisal to that accepted in TA658 does not reflect the evidence provided to the Committee and is unreasonable.

**THE DETERMINATION OF THIS APPEAL**

Sanofi requests that this appeal should be determined at an oral hearing.

**REQUESTED OUTCOME FOLLOWING APPEAL**

Sanofi asks the Appeal Panel to return this appraisal to the Appraisal Committee for further consideration with the following directions to the Committee and to NICE:

* In circumstances where, despite the clinical benefits, it is not possible to demonstrate cost effectiveness of isatuximab in combination even at zero price, when applying NICE’s standard methodology following the 2022 revisions, the process needs to be applied flexibly to ensure fairness. In particular:
  + The Committee must recognise that cost effectiveness cannot be achieved even at zero price;
  + The Committee must explain how it has taken into account the fact that components of the combination were appraised and recommended under a different methodology and in accordance with a higher ICER threshold
  + The Committee is not bound to make its decision on the reference case analysis, simply because pomalidomide and dexamethasone have been found to be cost effective under previous NICE methodology and it should instead give due consideration to the non-reference case analyses
  + The Committee should reconsider its approach to the modelling of efficacy of isatuximab in combination relative to pomalidomide and dexamethasone and should adopt a consistent approach to modelling of efficacy of daratumumab
  + The Committee should adopt a consistent approach to modelling of utilities in this appraisal relative to TA658
* NICE must refer isatuximab in combination to NHS England for commercial negotiation.

1. https://www.sheffield.ac.uk/nice-dsu/methods-development/not-cost-effective-ps0#:~:text=In%20a%20National%20Institute%20for,effective%20use%20of%20NHS%20resources. [↑](#footnote-ref-2)