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XXXXXXXXX

Sanofi

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Friday 2 August 2024

Dear XXXXXXXXXX

**Re: Final Draft Guidance — Isatuximab with pomalidomide and dexamethasone for treating relapsed and refractory multiple myeloma [ID4067]**

Thank you for your letter of 25 July 2024 responding to my initial scrutiny views. This is my final decision on initial scrutiny.

I assess each of your points in turn.

***Ground 1(a): In making the assessment that preceded the recommendation, NICE has failed to act fairly***

# Appeal point 1(a).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

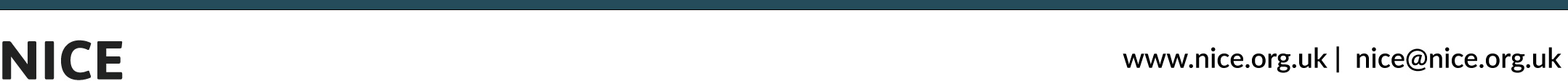
Having considered the additional arguments made in your letter of 25 July 2024, I agree that this is a valid appeal point as it relates to whether the Committee’s conclusions in relation to the fact that Isatuximab plus pomalidomide and dexamethasone is not cost effective, even if Isatuximab is supplied at zero price, are fully transparent and explained in the FDG.

I anticipate the appeal panel will wish to explore whether the Committee agreed that cost effectiveness based on standard methods was impossible (which appears to me to be the case: see FDG para 3.17) and, if so, whether it gave an adequate explanation in the FDG of how this impacted its decision making.

# Appeal point 1(a).5: The Appraisal Committee failed adequately to consider the non-reference case analyses submitted by Sanofi

Having considered the additional arguments made in your letter of 25 July 2024, I remain of the view that the remainder of this appeal point should not proceed to an oral hearing. That is because:

1. With regard to the decision not to consider generic pomalidomide prices expected to follow patent expiry later in 2024, I explained in my initial scrutiny why I was not minded to refer this



point, with reference to paragraph 4.4.4 of the Manual and the established position that the Committee can only consider the evidence that is presented to it. I noted for completeness that, despite that usual position, the Committee took a flexible approach by modelling cost effectiveness that included potential discounts for generics (so did in fact take into account future generics pricing as part of the evidence). Your letter of 25 July 2024 responds to that issue alone, appearing to argue that the modelled improvement to cost effectiveness due to the potential discount should have been considered or handled differently by the Committee in some way. This is not an answer to my reasoning in my initial scrutiny letter, which is that there was in my view no obligation under the Manual or as a matter of procedural fairness for the Committee to consider potential future discounts. I remain of that view so this argument will not be referred to the appeal panel.

1. With regard to the Committee's decision to reject a non-reference case approach proposed by the Company, I understand from your response that your argument here is distinct from your point 1(a).6 (which challenges the Committee's decision not to base its decision on the non- reference case) and is instead that the Committee failed to consider, or failed to give "further consideration", to the non-reference case analysis. In other words, I understand this as a procedural fairness argument that the Committee failed to take into account relevant evidence. In my view this is unarguable, as paragraph 3.17 of the FDG states in terms that the Committee was aware of and was able to consider this analysis alongside the reference case analysis for context, and that the Committee considered an adjusted version of that analysis again after consultation. For completeness I note you do not explain what "further consideration" you say would satisfy the requirements of procedural fairness. Arguments as to whether appropriate *weight* was afforded to the evidence such a point would fall under ground 2, not 1(a), and that is not how I understand this point.

***Ground 2: the recommendation is unreasonable in the light of the evidence submitted to NIC***

# Appeal point 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

Having considered the additional arguments made in your letter of 25 July 2024, I remain of the view that this appeal point should not proceed to an oral hearing.

As noted in my initial scrutiny letter, I did not refer this appeal point as your appeal did not appear to present an arguable case that NICE's approach or its decision as explained in detail at paragraph 3.17 of the FDG was unreasonable in light of the totality of the evidence put to NICE.

As a general point, there are several scenarios under which clinically effective technologies may be found not to be cost-effective even if they are zero priced. There may be costs associated with delivering the technology which remain even when the price is reduced to zero and these costs alone may outweigh the health benefits achieved. Even in the situation where a clinically effective technology can be acquired and delivered for zero cost, there are scenarios in which that technology may fail to demonstrate cost-effectiveness because it increases other aspects of resource use.

In your letter of 25 July 2024 you suggest that, because the Committee accepted Isatuximab in combination demonstrates clinical benefits over standard treatment, it was unreasonable for the Committee to apply standard methodology under which the combination cannot achieve cost effectiveness at zero price. You also suggest that a decision not to recommend a drug that is more effective than standard treatment "is clearly contrary to the interests of patients and the NHS as well as Sanofi and is therefore perverse".

These arguments seem to rely on the premise that any decision by NICE not to recommend a treatment that is more effective than standard treatment is unreasonable. That would seem not to recognise that appraisals are carried out in exercise of NICE's statutory power to evaluate both the benefits and costs of a health technology in accordance with NICE’s published methods and processes, which themselves make clear that appraisals are evidence-led and that not all clinically effective treatments will be recommended.

NICE appraisals aim to result in recommendations on what treatments the NHS should provide, given its financial constraints, in a robust, predictable and evidence-based way. They relate to the allocation of limited health resources between competing priorities and across all patients (not just those with the condition relevant to a given topic) all of which will be deserving in their own right. As explained in NICE's Manual (para 6.3.1),:

"Given the fixed budget of the NHS, the appropriate maximum acceptable ICER to be considered is that of the opportunity cost of programmes displaced by new, more costly technologies."

In other words, if NICE recommends a treatment, then the money spent on that treatment will not be available to spend on other treatments.

It is therefore critical that NICE follows fair and transparent procedures when making these difficult decisions, and that where there those procedures afford discretion to NICE's expert independent Committees they act reasonably in light of the evidence submitted to them.

I see no reason that NICE must, as a matter of *reasonableness*, adjust its usual processes to allow for a positive recommendation because a treatment that is not cost effective at zero price shows benefits. I am not persuaded that the Committee's approach, which appears to me to demonstrate a logical consideration of the evidence as explained at paragraph 3.17, was arguably unreasonable in the sense that it was obviously and unarguably wrong, illogical, or 'does not add up'.

# Appeal point 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

Having considered the additional arguments made in your letter of 25 July 2024, I agree that this is a valid appeal point. While I consider the Committee did take into account the relevant evidence and provided adequate reasons in the FDG (both of which arguments would fall under ground 1(a) in any event), I consider it an arguable point for the appeal panel to explore whether the committee's approach was unreasonable in light of the totality of the evidence.

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

Having considered the additional arguments made in your letter of 25 July 2024, I agree that this is a valid appeal point. While I do not consider a difference in approach between appraisals to be enough for an arguable unreasonableness point, I am satisfied that there is an arguable point for the appeal panel to explore whether the committee's approach was unreasonable in light of the evidence in this appraisal.

Conclusion

Therefore the valid appeal points are:

* 1(a).1 as it relates to transparency and whether the reasoning in the FDG was adequate;
* 1(a).2;
* 1(a).3 as it relates to the Committee's consideration of the application of flexibility to its own appraisal methodology;
* 1(a).4 as it relates to whether the Committee provided an adequate explanation for why a commercial negotiation was refused;
* 1(a).5 as it relates to the Committee's decision not to consider value attribution;
* 1(a).6;
* 2.2;
* 2.3 as it relates to whether the committee's approach was unreasonable in light of the totality of the evidence;
* 2.4;
* 2.5 as it relates to whether the committee's approach was unreasonable in light of the evidence in this appraisal.

NICE shares the valid appeal grounds of each appellant with the other appellants to assist with preparation for the hearing.

NICE will be in contact with you regarding the administration of the appeal, which will be held orally.

Yours sincerely

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Sharmila Nebhrajani OBE

Non-Executive Director & Chairman

National Institute for Health and Care Excellence