FAO XXXXXXXXX

XXXXXXXXXX, UK and Ireland

Ipsen Limited

Sent by e-mail only: XXXXXXXXXXXX

6 July 2023

Dear XXXXXXXXXX

**Re: Final Draft Guidance Document –** **Cabozantinib for previously treated differentiated thyroid cancer unsuitable for or refractory to radioactive iodine [ID4046]**

Thank you for your letter of 29 June 2023, lodging an appeal against the above Final Draft Guidance Document (FDG).

Introduction

The Institute's appeal procedures provide for an initial scrutiny of points that an appellant wishes to raise, to provide an initial view on whether they are within the permitted grounds of appeal ("valid") and are at least arguable. The permitted grounds of appeal are:

* 1(a) NICE has failed to act fairly, or
* 1(b) NICE has exceeded powers;
* (2) the recommendation is unreasonable in the light of the evidence submitted to NICE.

This letter sets out my initial view of the points of appeal you have raised: principally whether they fall within any of the grounds of appeal, or whether further clarification is required of any point. Only if I am satisfied that your points contain the necessary information, are arguable, and fall within any one of the grounds will your appeal be referred to the Appeal Panel.

You have the opportunity to comment on this letter in order to elaborate on or clarify any of the points raised before I will make my final decision as to whether each appeal point should be referred on to the Appeal Panel.

Initial View

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 1a.1: "The committee's decision to selectively use utility values from two different sources for the PFS and PD health states is arbitrary, biased, flawed and inconsistent with the NICE Methods Manual."**

I understand your argument under this ground 1(a).1 to be that the Committee has acted unfairly by using a utility value from the COSMIC-311 trial for progression-free survival (PFS) and a utility value from a vignette study for the progressed disease (PD) health state. Your position is that this approach is (1) illogical' (2) lacks scientific rationale; and (3) "it is not stated that this inconsistent approach is allowed in Section 3.9 of the NICE Processes and Methods Manual".

Your first two arguments would form the basis of a Ground 2 appeal point, rather than a Ground 1 appeal point. I have therefore considered them below, under Appeal point 2.2 (which I am minded to refer to the Appeal Panel as a valid appeal point).

As to your third argument, I have considered the Committee's explanation, in paragraph 3.9 of the FDG, of the bases on which it decided to use utility values from different sources. I also note that paragraph 4.3.8 of NICE's Health Technology Evaluations Manual does envisage the use of different EQ-5D utility values, as follows:

*Clearly explain the justification for choosing a particular data set. When more than 1 plausible set of EQ-5D data is available, sensitivity analyses should be done to show the effect of the alternative utility values.*

In light of this provision, I do not consider it arguable that the Committee has acted *unfairly* in adopting the different utility values. Such an approach is expressly anticipated by the Manual, in appropriate circumstances. Whether or not the approach was reasonable, is for consideration under Ground 2.

I am therefore not minded to refer this appeal point 1(a).1 to the Appeal Panel.

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

**Appeal point 2.1: "The committee has failed to take a balanced view of the strengths and weaknesses of the survival extrapolation methodologies in the modelled population and that of expert opinion alongside it."**

I understand your argument under point 2.1 to be essentially that, having acknowledged the uncertainty around the Overall Survival models produced by both the EAG and the Company, it was unreasonable for the Committee to then adopt the EAG model, having rejected the Company's blended survival analysis.

In particular, I note the Committee's reasoning in paragraph 3.7 of the FDG, in which it states:

*The committee noted the lack of transparency around the* [Company's] *blended survival analysis. Because of this the committee concluded that the exponential function used by the EAG for modelling OS in both treatment arms was preferable for its decision-making."* (emphasis added)

I agree that having noted the uncertainty around the EAG model, it is arguably unreasonable for the Committee to conclude that it should nevertheless use the EAG model, because of its concerns about the transparency of the Company's blended survival analysis.

I am therefore minded to refer this Appeal Point to the Appeal Panel.

I also note your acknowledgement that the Company was unable to answer certain questions from the Committee about the blended sensitivity analysis during the second committee meeting, and that the Company "*would have been happy to provide these answers afterwards but the NICE appraisal does not allow this in our experience and the chair wanted the answer in the meeting that day*". I anticipate this may be an area that the Panel will wish to explore during the hearing.

**Appeal point 2.2: "The committee’s decision to selectively use utility values from two different sources for the PFS and PD health states unreasonable as it is arbitrary, biased, flawed and inconsistent with the NICE Process and Methods Manual (PMG36)."**

As noted in my response above to appeal point 1(a).1, I understand your argument here to be that it was unreasonable for the Committee to adopt utility values from different sources for PFD and PD health states.

I note the Committee's detailed explanation of its reasons for doing so in paragraph 3.9 of the FDG. Nevertheless, I agree that this is arguably unreasonable and am minded to refer this appeal point to the Appeal Panel.

**Appeal point 2.3: " The committee’s decision that dose intensity should not be used instead of compliance despite precedence set in TA535 for lenvatinib because cabozantinib is flat priced is inconsistent with the previous DTC appraisal (TA535) and unreasonable."**

I understand your argument here to be that it was unreasonable for the Committee not to adopt a 'relative dose intensity approach' to calculating the drug acquisition cost for the NHS, because appraisal TA535 had used the relative dose intensity approach in similar circumstances.

The Committee's explanation for not adopting the relative dose intensity approach is that it would not reflect the true drug acquisition cost, in circumstances where cabozantinib is 'flat-priced' which I understand to mean that each tablet/capsule is the same price, regardless of its strength.

I do not currently understand you to be disputing that the method adopted by the Committee is a more accurate way of calculating the drug acquisition cost to the NHS. In those circumstances, I do not consider it arguably unreasonable for the Committee to have adopted that approach. Although a previous Committee did adopt the relative dose intensity approach in similar circumstances, that does not set a precedent or bind the Committee in this case. Two committees may reasonably reach different conclusions when faced with the same question. I note that in this case the Committee has explained why it has reached that different view; i.e. that in the circumstances of this evaluation, the relative dose intensity approach would not properly reflect the drug acquisition cost to the NHS.

I am therefore not minded to refer this Appeal Point to the Appeal Panel.

**Appeal point 2.4: " The committee has failed to consider the challenges in generating data for a rare disease in line with Section 6.2.34 of NICE Process and Methods Manual (PMG36)."**

I understand your argument here to be that the Committee's conclusion was unreasonable because it did not expressly consider the difficulties in generating data for a rare disease, given the small (c.80 patients) population in question.

I note, however, that at paragraph 3.13 of the FDG, the Committee does set out its thinking on this issue:

*The committee noted that the size of the population estimated to have treatment for this indication per year was small (see section 3.1). Even so, the committee understood that enrolment of people to the COSMIC-311 trial was sufficient to generate an analysis population. The company also confirmed in response to consultation that the second-line population represented the majority (approximately 76%; see section 3.3) of the ITT population in the COSMIC-311 trial. It also confirmed that the trial was powered to detect a difference in PFS for the second-line patient population. The committee understood that evidence generation did not appear to have been particularly difficult as a result of a small population size.*

That being the case, it seems clear that the Committee did pay careful attention to the challenges of generating evidence for this disease specifically. I also note that you have not argued for any particular additional steps that in your view the Committee should have taken, or any particular difficulties arising from particular characteristics shared by the patient population in question.

In light of the above, I am not minded to refer this Appeal Point to the Appeal Panel.

I note that a related point as to the likelihood of decision error and its consequences, which is affected by the small population size, is covered separately in Appeal Point 2.6 below.

**Appeal point 2.5: "The committee’s conclusions and decision making regarding the ICER threshold for this appraisal do not take into account all the factors identified in NICE’s Methods Guide."**

I understand your argument here to be that the Committee's conclusions were unreasonable because they did not take (and could not have taken) account of submissions from patient organisations or patient experts, because no such submissions were made, and no patient organisations or patient experts attended either Committee meeting.

I note that the final stakeholder list identifies 19 patient groups as stakeholders, who will all have been invited to participate throughout. It does therefore seem clear that NICE sought to include the patient perspective and so met its obligations under the Manual. In the circumstances it is not clear what further steps the Committee could or should have taken. In light of the above, I am not minded to refer this Appeal Point to the Appeal Panel.

**Appeal point 2.6: "The committee’s conclusions regarding the appropriate ICER threshold for this appraisal do not assess uncertainty in a balanced way nor do they take into account the likelihood of decision error and its consequences in accordance with NICE’s Methods Guide."**

I understand your argument here to be that the Committee's conclusion is unreasonable, because it does not properly take into account the "likelihood of decision error and its consequences". In particular, you argue that the likelihood of decision error is low, and that the negative impact (i.e. consequence) of decision error would be small, given the small population size.

Noting the small population size and relatively narrow range of potential ICERs in play, and the absence of specific consideration of this issue in the FDG, I agree that this is arguably unreasonable, and am minded to refer this Appeal Point to the Appeal Panel.

**Appeal point 2.7: "The committee’s conclusions regarding the plausible ICER and maximum acceptable ICER thresholds is unreasonable as it is arbitrary and mired in obfuscation."**

I understand your argument here to be that the Committee appears to have changed its views on the appropriate ICER threshold during the course of the appraisal but that the reasons for those changes and for the Committee's conclusions are unclear and that without clear explanation, that conclusion is unreasonable.

I note that the Committee's view as to the appropriate threshold did change as the appraisal progressed, as follows:

* "the low £20,000's per QALY gained" on 20 March 2023,
* the "lower end" of the £20,000 to £30,000 range on 4 April 2023,
* "the middle" of that range on 15 May 2023, and
* "the lower half" of that range on 15 June 2023 in the FDG.

You note that the Committee did not change any of its preferred assumptions during that period. It seems plausible to me that the Committee may not have changed any of its preferred assumptions over that period but did change its view of other elements such as uncertainty. However I cannot see that explained in the FDG.

Accordingly, I am minded to refer this Appeal Point to the Appeal Panel.

Conclusion

The above sets out above my initial views on all of your appeal points.

In respect of your points which I am not minded to refer on you are entitled to submit further clarification and/or evidence to me within the next 10 working days, and I will then give a final decision on the points to put before an appeal panel. For the points I am already content to refer on, an oral appeal will be held remotely.

Once I have made my final decision, and where there is more than one appellant, each appellant will receive the valid appeal points of the other appellants and their redacted appeal letter. This is to enable appellants to avoid duplication at the hearing where there are overlapping appeal points. If the appeal letter and/or responses to scrutiny contain confidential information please ensure you have provided a version with this information redacted by 27 July 2023.

Ordinarily appeals are conducted on the basis of the appellants’ written appeal letters, and the material generated during the appraisal process. Use of additional written material is discouraged, and the panel cannot receive any new evidence. If, exceptionally, you feel there is written material that will not be before the panel that you would wish to rely on you must let the NICE Appeal team know by return of letter, indicating what the material is, why it is desirable to submit it, and when it will be available, by no later than 21 July 2023. Please note that the appeal panel cannot accept papers that are tabled late or ad hoc, as this affects the preparation of the panel and other parties for the appeal.

If you wish to respond to any of the points in the letter, please send your response to appeals@nice.org.uk by no later than 5pm on 20 July. If you do not intend to submit a response please confirm this by email to appeals@nice.org.uk by the same deadline.

Yours sincerely

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Dr Mark Chakravarty

Lead Non-Executive Director for Appeals & Vice Chairman

National Institute for Health and Care Excellence