Sent by e-mail only: XXXXXXXXXX

FAO XXXXXXXXXX

XXXXXXXXXXXX, UK and Ireland

Ipsen Limited

27 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**Re: Final Draft Guidance Document – Cabozantinib for previously treated differentiated thyroid cancer unsuitable for or refractory to radioactive iodine [ID4046]**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 20 July responding to my initial scrutiny views. This is my final decision on initial scrutiny.

I note your comments in respect of the appeal points that I was minded to refer to the appeal panel for the reasons explained in my initial scrutiny letter. I confirm those points will be referred to the appeal panel. Thank you for confirming that you accept my reasoning in that regard, save as relates to your appeal point 2.3. I consider your further submissions on point 2.3 below.

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

**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 remain of the view that this appeal point is not arguable and should not proceed to an oral hearing.

I appreciate Ipsen's frustration that a different approach to calculating costs was taken in previous appraisals that was potentially more advantageous to the company. However, the Committee was entitled to depart from that previous approach, provided it did so **fairly** (i.e. by complying with NICE's processes, giving Ipsen fair warning of its favoured approach and explaining its reasons) and **reasonably** (i.e. by adopting an approach that makes sense or "adds up" on the evidence that was available to it).

I have considered your arguments under both grounds 1(a) and 2.

I can see no arguable **unfairness** here under ground 1(a). While departing from the approach taken in previous similar appraisals, the Committee noted this expressly in para 3.11 of the FDG (quoted in your letter of 20 July) and explained why it had reached a different view. Therefore I disagree with the suggestion in your letter of 20 July that the Committee in this appraisal showed a "failure to take account of precedents". Further, the Committee told Ipsen in advance that the Committee was minded to take this approach and so Ipsen had an opportunity to make representations. Ipsen did so in the consultation on Draft Guidance, to which the EAG and Committee responded with reasons for the approach adopted (see page 8 of the second [Committee papers](https://www.nice.org.uk/guidance/gid-ta10932/documents/committee-papers-2)). There can therefore be no procedural unfairness argument that the Committee failed to give adequate reasons for, or fair warning of, the change in approach.

As to ground 2, I can see no arguable **unreasonableness** here. I note you disagree with my comment in initial scrutiny that the previous Committee's approach to calculating costs "does not set a precedent or bind the Committee in this case" . You consider this lack of binding precedent is unreasonable as it creates inconsistency and "*the goalposts can seemingly be moved at will by a NICE Committee*". I am not persuaded by this argument for the reasons set out in my initial scrutiny letter: a lack of consistency in itself (i.e. without some additional feature calling into question the validity of the different approach taken by the Committee) is not enough to show arguable unreasonableness (as that term is to be understood in the context of a NICE appeal and any public law argument made by way of judicial review).

I therefore considered whether there is any additional argumentation in your appeal submissions that arguably calls into question the validity of the approach taken by the Committee. I assume for this purpose that you may indeed be disputing that the method adopted by the Committee is a reasonable approach to calculating the drug acquisition cost to the NHS. I note that while your appeal submissions are focused on the inconsistency point that I have addressed above, you also state that "*the company used RDI because it believed it was the most appropriate way of deriving the true cost per cycle of cabozantinib*". I have considered that argument alongside the submissions made by Ipsen during the appraisal process and the responses to those submissions, in particular at page 8 of the second [Committee papers](https://www.nice.org.uk/guidance/gid-ta10932/documents/committee-papers-2) and pages 250, 414, 416 and 595 of the first [Committee papers](https://www.nice.org.uk/guidance/gid-ta10932/documents/committee-papers-2). Having done so, I remain of the view that there is no arguable case that the Committee's approach was unreasonable on the evidence available. That is in particular in light of the detailed consideration of the point by the EAG (at page 595 of the first Committee papers):

“*The EAG believes that given the flat pricing structure for cabozantinib, it is more appropriate to adjust cabozantinib costs according to the proportion of days on which patients received treatment (compliance), rather than the average amount of the planned dose received (RDI). For example, if a patient received treatment with 60mg cabozantinib for 15 days followed by treatment with a lower dose of 20mg cabozantinib for 15 days, there would be no cost savings to the NHS. The compliance-adjusted cost would appropriately reflect this scenario, whereas adjusting drug costs by RDI would erroneously suggest a cost saving of 33%. Regardless of precedents in previous NICE appraisals, the EAG believes that using compliance is more appropriate in this case.”*

The Committee explains why it agrees with this approach at 3.11 of the FDG. I can see no argument in the company's submissions in the appraisal or appeal that the chosen approach, whilst different from the company’s preferred approach, does not make sense or "add up" as an appropriate method of calculating cost. Therefore I will not refer this point to an appeal panel.

Conclusion

Therefore the valid appeal points are:

* 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**."
* 2.2 (originally 1(a).1 and 2.2): "**The committee’s decision to selectively use utility values from two different sources for the PFS and PD health states was unreasonable as it is arbitrary, biased, flawed and inconsistent with the NICE Process and Methods Manual (PMG36)**", as it relates to the argument that the Committee's approach of 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 was unreasonable because it: (i) is illogical and (ii) lacks scientific rationale.
* 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."**
* 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."**

NICE shares the valid appeal grounds of each appellant with the other appellants to assist with preparation for the hearing. In this case you, Ipsen, are the only appellant.

I note your comment that Ipsen wish to put on record that you consider there is an issue with patient organisation engagement in appraisals that NICE needs to investigate and address to ensure it remains as inclusive as possible in its decision making. I agree that it is enormously valuable to hear from patients in the appeal process. In addition to the comments in my initial scrutiny letter regarding how NICE sought to include the patient perspective in this appraisal, I would note that NICE has taken steps to accommodate the perspective of a patient organisation, the British Thyroid Foundation, that contacted NICE following publication of the FDG. While the British Thyroid Foundation cannot appeal the FDG, having chosen not to participate in the appraisal, I have invited them to attend and read out a statement at the beginning of the appeal hearing and hope this flexible approach will nevertheless enable the patient voice to be heard. I have also noted and passed on your concerns about patient organisation engagement in appraisals to NICE’s Director of Medicines Evaluation.

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

Yours sincerely

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Dr Mark Chakravarty

Lead Non-Executive Director for Appeals & Vice Chairman

National Institute for Health and Care Excellence