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Sent by email

[redacted]
Head of Health Outcomes
Sanofi
One Onslow Street
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22 November 2013

Dear [redacted]

Final Appraisal Determination: aflibercept for the treatment of metastatic colorectal cancer

Thank you for lodging Sanofi's appeal against the above Final Appraisal Determination. I have been informed by NICE's staff that the appeal was received slightly after the deadline for the appeal of 5pm on 14 November 2013. On this occasion I have agreed the appeal should be accepted, but for the future may I gently remind Sanofi of the importance of adhering to deadlines.

Introduction

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

- Ground 1: The Institute has failed to act fairly
- Ground 2: The recommendation is unreasonable in the light of the evidence submitted.
- Ground 3: The Institute has exceeded its powers.

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 and arguably 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 make my final decision as to whether each appeal point should be referred on to the Appeal Panel.

I can confirm that there will be an oral hearing of the appeal.

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Initial View

Ground 1

1.1. In concluding aflibercept did not meet the criteria for EoL therapy, the Committee has incorrectly applied the Supplementary Advice issued by the Institute.

You argue that the EoL supplementary advice require a three stage decision making process. First, there must be sufficient evidence to indicate an extension to life of normally three or more months (section 2.1). If that is satisfied then the Committee considers the technology in light of the special factors referred to in section 2.2 of the supplemental advice. Having done so, then the Committee considers whether the estimates for life extension considered under section 2.1 are robust.

You argue that the Committee instead considered whether there was evidence to indicate a sufficient extension to life, and then or at the same time considered whether the evidence for an extension to life was robust. As it did not consider that evidence to be robust it did not consider aflibercept in light of the special factors contained in the supplemental advice.

I note you accept that the Committee's approach has not altered the context of the substantive guidance in the FAD. That must be correct. You appear to be saying that the Committee should have considered whether or not section 2.2 of the supplemental advice might hypothetically have persuaded it to issue more positive guidance, albeit, and subject to your appeal point 2.2, it would then have gone on to say that the estimates for life extension were not robust and the positive guidance would not in fact be issued.

Not only does that get the Committee to the same position is reached in any event, but it seems to do so for the same reason, the only difference being that your approach requires the Committee to take a decision on criteria which it then does not implement. With respect, your approach to the supplemental guidance seems profoundly counter-intuitive. Section 2.3 of the supplemental advice seems to be very clearly to guide and inform the section 2.1 consideration, rather than being a stand-alone criterion. Nor do I think a committee can be obliged as a matter of fairness to reach a conclusion on what would be a hypothetical question.

I am not minded to agree this is a valid ground one appeal point.

1.2 The Committee's conclusions with respect to the appropriate time horizon are unclear and relevant evidence appears to have been disregarded

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I note your comment that the committee recognised at paragraph 4.14 (in a section discussing cost effectiveness) that a 15 year time horizon was appropriate. However I am not sure you accurately represent their view in that paragraph. They say

> "*The Committee was aware that the time horizon should be sufficiently long to capture all the costs and health benefits in the full population (that is, a lifetime horizon should be used.) the Committee therefore concluded that a time horizon of 15 years was, in principle, appropriate because all patients are likely to have died by 15 years; however, the Committee agreed that, when the time horizon is much longer than the trial duration, and the life expectancy of most patients, it is particularly important to explore the assumptions underlying how overall survival is extrapolated*."

There then follows a long paragraph discussing those assumptions and the associated uncertainty.

Paragraph 4.7 sits in a section discussing clinical effectiveness. The statement that an extrapolation period should reflect the time in which all patients will have died foreshadows the same sentiment in 4.14. The statement that a longer than five year survival for these patients is very unusual is factually correct (and is as modelled by you) and seems consistent with the statement in 4.14 that a 15 year time window "*is much longer than…the life expectancy of most patients*".

Paragraph 4.24 repeats the view that a 15 year time horizon is in principle appropriate, repeats the view that it introduces uncertainty, and, explicitly as a means to explore uncertainty, considered a shorter time horizon.

I see no evidence in the FAD that the Committee disregarded data submitted by your company.

The committee's reasoning appears clear enough for you to engage fairly with the appraisal process and I am not minded to conclude this is a valid ground one appeal point.

1.3 The Committee's conclusion that median survival is likely to be closer to 1.44 months than 4.7 months is unexplained and the basis for that view is unclear

A valid ground one appeal point.

1.4 The Committee has disregarded evidence indicating that improved survival may be attributed to improved medical management.

I agree the Committee appears to have accepted that resection of metastases in patients where they are confined to the liver has improved five year survival rates. I am less clear what the basis is for the assertion that they have concluded this is the

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sole factor. Nor do I see what the basis is for the committee having ignored the evidence you cite?

I am not currently persuaded there is a valid ground one point.

Ground 2

2.1 The Committee have incorrectly assumed that further follow up data from the VELOUR trial are available.

I note you believe that the Committee infer that you have withheld available data from them. I also note you say this is not the case. These are serious matters requiring public discussion and without expressing any further view on the matter I agree this appeal point should be considered by an appeal panel.

2.2 The Committee's conclusion that the data relating to aflibercept were not sufficiently robust to support a 3 month life extension benefit is inconsistent with available evidence and unreasonable

A valid ground 2 appeal point

2.3 The Committee has provided no explanation for the inconsistencies in its approach to assessment of overall survival benefit in this appraisal and TAG 242, these inconsistencies suggest an arbitrary approach which is unreasonable

I accept that lack of consistency of approach could support an argument of unreasonable guidance, although I note that the appeal ground is that the guidance should be unreasonable in light of the evidence submitted and not in light of other appraisals. I am therefore somewhat cautious about such arguments. A practical problem, which is reflected in the wording of the appeal ground, is that neither an appraisal committee nor an appeal panel can reasonably be expected to be familiar in detail with the evidence and reasoning in other appraisals. (I do note your comment that this was essentially the same committee as TAG 242. They may well have some memory of that appraisal, although I am not sure that would provide an adequately rigorous and transparent basis to bring considerations of that past appraisal into this one. However I do not think we can have different approaches to consistency with past appraisals depending on which committee conducted them. And even the same committee must apply its mind afresh to each appraisal.) Consistency can only be desirable between cases which are relevantly alike. It seems to me that differences in the quality of the evidence base mean appraisals are rarely relevantly alike, particularly when it is a judgment on the relationship between PFS and OS and how much life extension two different products studied in different trials might deliver.

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I am not minded to agree this is a valid appeal point.

2.4 The committee's rejection of utility data from the mCRC study in favour of an arbitrary estimate for progressed disease is unreasonable

I understand that you and the committee differ on utility values. I understand, at least in outline, the reasons for the respective views. What I am not clear about is why both views are not reasonable? I note the ERG value has been used in the past, and while I have said above that I doubt there is a requirement for consistency (at least at that level of detail), this does tend to suggest the value is within a reasonable range.

I am not minded to agree this is a valid appeal point.

As I agree some of your appeal points are valid they will be passed to an appeal panel for consideration. There will be an oral hearing. I would be grateful to receive your comments on the points I am presently not minded to treat as valid within 10 working day of this letter, no later than 5pm on **Friday 6 December 2013** whereupon I will take a final decision.

Yours sincerely

[redacted]
Appeals Committee Chair
National Institute for Health and Care Excellence