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Sent by email to [redacted]@solvingkidscancer.org.uk

5 August 2016

Dear [redacted] and [redacted]

Final Appraisal Determination: Neuroblastoma (high risk) – dinutuximab (maintenance after therapy) [ID 799]

Thank you for lodging Solving Kids' Cancer's appeal against the above Final Appraisal Determination (FAD). I have replaced Dr Helliwell as Vice-chair of NICE and her responsibility for initial scrutiny of appeals.

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:

- 1(a) NICE has failed to act fairly;
- 1(b) NICE has exceeded powers; or

- (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 and arguably fall within any one of the grounds will your appeal be referred to the Appeal Panel.

You will 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.

Initial View

Ground 1 (a)

1.1 Dinutuximab (Unituxin) should have been appraised through the Highly Specialised Technologies Programme. I am not minded to consider this a valid appeal point. I consider the critical point here to be that NICE is bound to consider a technology in accordance with the referral made by Ministers. Moreover, although it is correct that a request could have been made to Ministers for an appraisal process to be halted and another one started with an appropriate re-referral from Ministers, that would be a decision about the appraisal process taken outside the appraisal process rather than a decision about the treatment taken within the appraisal, which is the subject of this appeals process. Further, the scope for the appraisal under the single technology appraisal methodology was consulted upon and generally agreed at the start. The single technology appraisal process had also been used successfully to assess other drugs for relatively small populations, including paediatric cancer. Therefore I do not think it was unfair or unreasonable not to request a re-referral by Ministers.

1.2 NICE unfairly failed to apply its end of life criteria. I am not minded to consider this a valid appeal point. The ‘end-of-life criteria’ are set out in paragraph

6.2.10 of the Guide to the Methods of Technology Appraisal. They make no distinction between adults and children. It is not open to Appraisal Committees to vary the criteria, which are set by NICE's board and are binding on committees. It is clear from the FAD that the Committee considered the criteria but that dinutuximab did not meet the first of these (that treatment is indicated for patients with a short life expectancy, normally less than 24 months) given that life expectancy is four years. You also propose that the Appraisal Committee should have looked for sub-groups to which the end-of-life criteria could be fully applied. However, the only possible sub-group offered in evidence is set out at paragraph 3.4 of the FAD which relates to treatment benefit in groups with a Curie score of 0 or 1. But the company concluded that the very low numbers with a Curie score of 1 meant that the results should be treated with caution. No further evidence was supplied which would enable more robust assessment of a sub-group to fulfil the criteria in the second half of para 6.2.10. It is therefore hard to see how the process was unfair.

1.3 The analysis of ANBL0032, and specifically the resultant use of a 10-year cure point, was inadequately explored. I consider that your point has two parts. First the use of 2014 data, including the 10-year cure point and, second, that the Appraisal Committee did not directly consult members of the Clinical Oncology Group (COG) who were involved in the ANBL0032 trial. On the first of these, there is a full discussion in the Appraisal Consultation Document (ACD) about the different dates from which data could be drawn from the trial and its follow-up and their relative weaknesses and strengths. The Committee's conclusion was to take the longest data set from 2014 including opting for the 10-year cure point with which to assess the clinical effectiveness of dinutuximab. The issue was not whether dinutuximab was effective which the licensing authority had already considered but its relative effectiveness over existing treatment. This aspect of the ACD was subject to consultation and the points raised in that consultation were responded to when the Committee reached its final conclusion. It is difficult to see how the process in reaching the decision to use the 2014 data has been unfair and I am not therefore minded to consider this a valid appeal point. I consider below the ground 2 appeal on this point.

The second point is whether the Appraisal Committee should have sought the views of a COG clinician in considering the 2014 data and its use. Under the STA process the assembly and submission of evidence rests with the sponsoring company. It is then vetted and commented on by the Evidence Review group (ERG). If the company did not consider it necessary to have direct input from the COG and if the ERG did not point to a gap in evidence that only the COG could resolve it is difficult to see why the Committee should have sought evidence from the COG. The committee might have asked the COG for comment if it considered that would illuminate say a critical point of the study which seemed ambiguous or flawed, even if the COG were not on the consultee list. However, the usual practice is to rely on the written output of studies, not on the authors' direct input. So in the absence of such an obvious flaw and with the comments separately made in consultation and by experts in the field there seems no reason why the Committee should have sought views from the COG and I am therefore not minded to consider this a valid point.

Ground 1 (b) NICE has exceeded its powers

I consider this a valid appeal point. As it is a legal point and as the panel is not legally qualified (although it does have access to legal advice) it is important in the interests of fairness that all sides understand the respective legal positions in advance. Therefore I would ask that you provide a written submission on this point which can go to the panel and to the Appraisal Committee. The panel's legal advisor will then prepare his or her advice to the panel on this point in writing, which will also be shared with you and the Appraisal Committee before the decision is taken. You will be able to make a further written submission responding to the panel's legal advice as appropriate. In this way the panel will be able to prepare for its determination. Please can you provide the first submission by **Friday 26 August**. The panel's legal adviser will have 10 working days from receipt of that to prepare their advice to the panel, and you will have a further 10 working days to comment on that in advance of the hearing.

Ground 2

2.1 Dinutuximab should have been appraised through the Highly Specialised Technologies Programme. I am not minded to consider this a valid appeal point. As noted above, technologies that are suitable for the Highly Specialised Technologies programme are determined through the referral process, not by Appraisal Committees. It is therefore an issue of process rather than one of consideration of evidence put forward during an appraisal.

2.2 It was unreasonable for the Institute to use a 10-year cure point given the evidence before it. I am not minded to consider this a valid appeal point. The Appraisal Committee considered the 2014 data because this gave a fuller picture of outcomes and in doing so they adopted the 10-year cure point. They could have used an earlier data set and settled on a 5-year cure point but that would seem irrational given that later robust data was available that showed adverse events continued to occur after the 5-year point.

You say in your letter that the 'Committee chose an interpretation of the data that is not supported by the international neuroblastoma research community, is not in accordance with standard practice in the case of rare paediatric cancers, was not used or referred to by either the FDA or EMA'. I note that paragraph 4.3 of the FAD includes references to the EMA which considered that caution should be used in interpreting the event free survival results from the trial and that they requested the event free survival analysis from the 2014 data. For this to be a valid appeal point there would need to be evidence from the research community that the Committee's analysis of the data and the adoption of the 10-year cure point was unreasonable, for example in the form of their own published paper.

As I have agreed that there is at least one valid appeal point there will be in oral hearing to determine this, details of which will be separately communicated to you by the secretariat.

I will be happy to consider any further comment you may have on the points which I am not minded to regard as valid before making a final decision. Any such comments should be received by **Friday 19 August at 5pm**.

Yours sincerely

Andy McKeon
Vice chair
National Institute for Health and Care Excellence