Solving Kids' Cancer
CAN Mezzanine, 49-51 East Road
London, N1 6AH
T 020 7284 0800
Info@solvingkidscancer.org.uk
www.SolvingKidsCancer.org.uk

28th July 2016

Dr Margaret Helliwell
Vice Chair
National Institute for Health and Care Excellence
10 Spring Gardens
London SW1A 2BU

Re: Final Appraisal Determination – dinutuximab for treating high-risk neuroblastoma

Dear Dr. Helliwell,

Solving Kids' Cancer hereby gives notice that it would like to appeal against the Final Appraisal Determination for "Neuroblastoma (high-risk) - dinutuximab (maintenance, after therapy) [ID799]" on the following grounds.

1) NICE failed to act fairly and exceeded its powers; and

2) The recommendation is unreasonable in light of the evidence submitted to NICE.

Anti-GD2 antibody is now widely accepted as being established as a standard of care for the treatment of high-risk neuroblastoma. Dinutuximab is the only drug ever approved for the treatment of this disease, gaining both FDA and EMA marketing authorisation approval. Failure to recommend dinutuximab for use on the NHS threatens to leave children across the United Kingdom behind the rest of the world in treating this devastating and deadly disease that affects a very small number of the most vulnerable in our society. In fairness to these children, NICE must ensure that it has properly evaluated all of the evidence regarding dinutuximab, anti-GD2 antibody therapy in general, the unique challenges faced by clinicians treating high-risk neuroblastoma, and the academic-led research landscape. The straightforward

pharmacoeconomic approach of the Single Technology Appraisal (STA) process, leaving many unidentified, intangible, or unquantifiable benefits, is not the correct framework for assessing treatments within these contexts.

Failure to recommend the product as a cost-effective use of NHS resources may result in UK clinicians and researchers being forced to abandon anti-GD2 antibody maintenance therapy. Whilst it remains the clear view of the international scientific community that this therapy saves the lives of children, families will do whatever it takes to ensure their children are able to receive it. This could very well require GBP 500,000 per child being raised through public appeals in order to access treatment abroad. Whilst this is not money spent by the NHS *per se*, it will be UK taxpayers who ultimately provide it, and it will be lost to the UK economy. With a clear precedent for this existing in the period before anti-GD2 antibody therapy first became available in the UK, this is not scaremongering. If anti-GD antibody therapy is not available in the UK – something that can only be secured for certain with positive NICE guidance on dinutuximab, it is precisely what will happen.

We therefore consider it essential that NICE appraises dinutuximab with a particular focus on the product and its particular circumstances and the source and nature of the data that underpins its use.

Solving Kids' Cancer has several concerns that it wishes to raise in appeal. First, it challenges the Appraisal Committee's approach to this technology appraisal. We consider that its use of the STA process was both unfair and unreasonable given the nature of the product and the disease it treats. It has long been acknowledged that the Institute's standard approach to technology appraisal does not suit products such as dinutuximab and its use in very rare, typically end-of-life diseases, such as high-risk neuroblastoma. That is why the Institute introduced the Highly Specialised Technology (HST) appraisal process. To continue to appraise dinutuximab using the STA process - which would almost inevitably lead to a negative recommendation for dinutuximab - when the HST process was available, was unfair and unreasonable. NICE could have taken a number of steps to ensure that it appraised dinutuximab on the correct basis and it was unfair that it did not.

Our second basis for appeal is that, it was inappropriate for the Institute to select a 10-year cure point from the March 2014 data cut as the basis for effectiveness. The Appraisal 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, and about which there was no expert opinion or insight available to enter into meaningful dialogue with the ERG, or indeed the Committee itself.

The decision also infringes the rights of the child.

Since the above give rise to outcomes that we believe are both unreasonable and unfair we have appealed the same points under both Ground 1a and Ground 2.

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

1.1(a) Dinutuximab (Unituxin™) should have been appraised through the Highly Specialized Technologies Programme

Undertaking to appraise dinutuximab as a Single Technology Appraisal (STA) was unfair. The Highly Specialised Technologies (HST) Programme is clearly a more appropriate mechanism, as evidenced by the Institute's Process and Methods Guide.

> *"36. Given the very small numbers of patients living with these very rare conditions a simple utilitarian approach, in which the greatest gain for the greatest number is valued highly, is unlikely to produce guidance which would recognise the particular circumstances of these very rare conditions. These circumstances include the vulnerability of very small patient groups with limited treatment options, the nature and extent of the evidence, and the challenge for manufacturers in making a reasonable return on their research and development investment because of the very small populations treated."*

Given the clear consensus that evaluation of dinutuximab as an STA could not take into consideration the particular challenges, contexts, research landscape, and drug development issues surrounding treatment of high-risk neuroblastoma (and indeed paediatric cancer in general), it is unreasonable for the Institute to appraise the product on the basis of standard STA methodologies, knowing that the result was always likely to be negative. As Sir Andrew Dillon, Chief Executive of NICE himself stated "*in evaluating* [HST] *drugs, NICE takes into account a greater range of criteria about the benefits and costs of HSTs than is the case with its appraisals of mainstream drugs and treatments. This is because applying our standard approach to treatments for very small groups of patients would result in us always recommending against their use. This would be unfair.*"[1]

[1] http://www.channel4.com/programmes/nhs-2-billion-a-week-counting/articles/all/nices-role-in-nhs-funding/3101

Solving Kids' Cancer considers that the Committee or indeed the NICE team running the appraisal should have considered this and, at a minimum, should have notified the relevant stakeholders that it may have been more appropriate for the review to be conducted *via* the HST route, and acted accordingly. Solving Kids' Cancer accepts that the Institute is to some extent constrained by the directions it receives from the Secretary of State, but there have been numerous instances where NICE has shown some flexibility and we consider that it should have done so in these circumstances, in the interests of patients. For example, NICE could have acted in a number of different ways:

- It could simply have decided that the appraisal should have been conducted using HST methods. We are aware of a number of instances where NICE has taken a flexible approach, e.g. by applying a multi-technology appraisal (MTA) approach to an STA and *vice versa.*

- It could have suspended the current appraisal to allow United Therapeutics to take steps to modify the basis for the technology appraisal. There have been numerous instances where NICE has suspended an appraisal pending further clarifications with the Department of Health or specialist commissioning boards.

- It could have approached the relevant Minister to request that the terms of the referral to NICE should be modified. We note that the NICE topic selection process for technology appraisals (TA) and highly specialised technologies (HST) (see https://www.nice.org.uk/media/default/About/what-we-do/our-programmes/Topic-selection-and-scoping-flowchart-July-2014.pdf) makes clear that it is "*NICE, Department of Health and NHS England* [that] *jointly agree on topics to seek Ministerial referral*" at Decision Point 4 (post-scoping) in the HST process. We see no reason why the Institute could not have approached the relevant Minister to explain that the dinutuximab appraisal should rightly have been conducted as an HST and sought the Minister's referral on that basis.

1.2(a) NICE unfairly failed to apply its end-of-life criteria

The decision not to recommend dinutuximab was based on a conclusion that "*dinutuximab does not represent a cost-effective use of NHS resources…*" (paragraph 4.23). However, the Committee did readily accept that "*2.81 life years (approximately 33.7 months) were gained for the dinutuximab regimen compared with isotretinoin alone*" (paragraph 4.22); *i.e.* that on average patients could expect to live for nearly 3 years longer if treated with anti-GD2-based immunotherapy rather than retinoic acid maintenance alone. Further, the Committee stated that "*the dinutuximab regimen appears to confer a small event-free survival advantage and overall survival advantage compared with isotretinoin…*" (paragraph 4.23). The Committee went on to say in the same paragraph that "*a case remains for accepting a higher ICER for a patient population of children and young adults to account for the uncaptured health-related benefits of treatment. However, the ICER was too high to allow it to recommend the dinutuximab regimen, even when taking into account other aspects of health-related quality of life not adequately captured in the QALY.*"

Notwithstanding this position, NICE failed to apply its special end-of-life criteria in a way that is appropriate for children and takes into account their best interests. The reason stated for this was because the median life expectancy of patients with high-risk neuroblastoma of 4 years is greater than the stated threshold of 24 months and therefore these special criteria could not be applied (paragraph 4.21). NICE also seemed to rely on an earlier approach not to apply the guidelines in relation to an appraisal for mifamurtide. However, what is not said is that mifamurtide received a positive recommendation and so at least some children could benefit. This is not the case here when there is an out-right negative recommendation. Further, as highlighted in a recently published response to the draft NICE decision,[2] the implications of 4-year life expectancy for a 3-year-old child are not the same as those for adult patients and the question needs to be asked whether it is appropriate to apply the end-of-life criteria to children in the same way as to adults. On the facts, we would argue that children must be afforded greater protection under this policy since they are a particularly vulnerable group. NICE should have applied its end-of-life criteria to children (or at least considered whether there is a sub-group since page 40 of the FAD says "*The committee concluded that for most patients with high-risk*

[2] Adamson PC, Park JR, Pearson AD. When Life Expectancy is Not Short Enough: A Perspective on the National Institute for Health and Care Excellence (NICE) Preliminary Guidance for Dinutuximab. Pediatric Blood & Cancer. 2016 Jan 6.

neuroblastoma, dinutuximab does not fulfil the criterion)" meaning of course that for some, the criteria would apply.

By applying an across-the-board approach to the policy, NICE has acted unfairly. NICE has also acted unfairly by failing to investigate whether the end-of-life criteria could be applied to a sub-group of patients despite clear evidence that some might benefit. Frankly, its failure to do so is simply shocking.

1.3(a) The analysis of ANBL0032, and specifically the resultant use of a 10-year cure point, was inadequately explored.

The interpretation of the results of the Children's Oncology Group (COG) randomized control trial ANBL0032 was unquestionably pivotal in establishing the efficacy of dinutuximab, and therefore the number of QALYs gained. In selecting a 10-year cure point from the March 2014 data cut as the basis for effectiveness, the NICE Committee chose an interpretation of the data that is not supported by the international neuroblastoma research community, is not in accordance with standard practise in the case of rare paediatric cancers, was not used or referred to by either the FDA or EMA, and about which there was no expert opinion or insight available to enter into meaningful dialogue with the ERG, or indeed the Committee itself.

There was a very apparent lack of understanding and appreciation of the ethical considerations and practical issues when conducting trials in a paediatric cancer that has few potential subjects for trial and high mortality. ANBL0032 was a large and ambitious trial by rare disease standards – the COG is a clinical trials collaborative group of 200+ institutions across North America. It enrolled patients for more than 8 years before it was stopped early for efficacy, being able to show a 2-year Event Free Survival (EFS) advantage in favour of the dinutuximab arm. This is standard research practise in rare paediatric cancers, where recruiting sufficient numbers of patients is inherently difficult due to incidence of disease; trials are designed to detect differences in 2 or 3-year EFS, and/or 5-year Overall Survival (OS).

Peter Adamson, Chair of Children's Oncology Group commented on the use of March 2014 follow-up data thus, "*The fact that such data were readily available reflects the commitment of the academic pediatric cancer community to continue to follow patients for many years following original diagnosis. The 2014 results, which were not part of the original statistical design and thus not necessarily powered to*

answer the question posed, found a smaller event-free survival advantage (59.3% vs. 48.3%, P = 0.15) and overall survival advantage (75.1% vs. 61.0%, P = 0.03)."

NICE's Guide to the methods of technology appraisal sets out a clear hierarchy in terms of the evidence that the Institute may consider during a technology appraisal, with data from randomized controlled clinical trial data clearly at the top of that hierarchy. While we accept that the Committee may take into account other sources of evidence, the courts have made clear that this discretion is not unfettered, e.g. the *Servier* case established that the Appraisal Committee needs to give clear reasons for reaching a different view from the European Medicines Agency whose view must be accorded respect.

In appraising this treatment, NICE has a duty of care to both children in the UK affected by this devastating and deadly disease, and their families, to ensure that it is fully cognisant of all of the available evidence, and expert interpretation thereof. As such it should have sought engagement with all prevailing expert opinions, and consequently acted unreasonably in failing to seek direct input from the Children's Oncology Group (COG) on such a pivotal matter. This was particularly important since ANBL0032 was not a study undertaken by United Therapeutics, but by COG, and should have been scrutinised accordingly with *their* input. The Committee acted unfairly in failing to reach out to COG for comments regarding the use and interpretation of data from its study.

Ground 1b - NICE has exceeded its powers

For the reasons described under Ground 1.2(a) above (*i.e.*, unfair application of NICE's end-of-life policy), there has been a breach of Section 11 of the Children Act 2004[3] coupled with the need pursuant to Article 3 of the UN Convention on the Rights of the Child to take the best interests of children into account as a primary consideration. Also, there can be no doubt that as a public body, NICE is bound in its appraisals to take account of human rights legislation. There are numerous references to this obligation in NICE guidance: see, for example, the NICE Guide to Methods of Technology Appraisals also the Social Value Judgments principles. We submit that NICE has breached the Convention in relation to the following articles: Article 2 (the right to life); Article 3 (the right not to be subject to inhuman or degrading treatment); Article 8 (the right to private and family life); and Article 14 (the right not to be discriminated against in the enjoyment of other Convention rights).

[3] http://www.legislation.gov.uk/ukpga/2004/31/pdfs/ukpga_20040031_en.pdf

We are aware that NICE has considered human rights aspects in the past, including in appeals involving Celgene and BMS, for instance, but as far as we are aware those appeals have not specifically considered the issues as they apply to children. Moreover, those points have not yet been addressed by a court.

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

Regarding our Ground 2 appeal points, it is important to note that the human rights context of this appeal also impacts upon the approach taken to Ground 2, perversity. This is because the more substantial the interference with human rights, the more is required by way of justification before NICE should accept that the decision is a reasonable rather than a perverse one. This approach is now well established in the case law: see, in particular, *R v Ministry of Defence, ex p. Smith* [1996] QB 517, 554 per Sir Thomas Bingham MR; see also in a healthcare context *R (Rogers) v Swindon NHS Primary Care Trust* [2006] 1 WLR 2649, § 56 "*... the case is concerned with a decision which may be a life or death decision for the claimant. In these circumstances .... it is appropriate for the court to subject the decision to refuse funding for the treatment (and thus in practice the treatment) to rigorous scrutiny.*"

2.1 Dinutuximab should have been appraised through the Highly Specialized Technologies Programme

For the reasons set out in 1.1a above, the NICE Appraisal Committee acted unreasonably by pursuing a Single Technology Appraisal process for a product and use, when in the words of its own Chief Executive "*our standard approach to treatments for very small groups of patients would result in us always recommending against their use.*"

2.2 It was unreasonable for the Institute to use of a 10-year cure point, given the evidence before it

In selecting a 10-year cure point from the March 2014 data cut as the basis for effectiveness, the NICE 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, and about which there was no expert opinion or insight available to enter into meaningful dialogue with the ERG, or indeed the Committee itself. As a parent focused charitable organisation we now find ourselves in a position where the clinical and research community, in whom parents must have absolute trust and confidence, are saying one thing, and NICE in their appraisal of dinutuximab are clearly indicating another. We can only conclude that the approach NICE has taken to this appraisal is unreasonable in light of the evidence before it.

Please let us know if you have any comment or queries, or require any clarification on any of these grounds for appeal.

Yours sincerely

, Chief Executive

Chair of Trustees