NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA/MTA)

APN311 for treating high-risk neuroblastoma

Response to consultee and commentator comments on the draft scope

Comment 1: the draft remit

Section	Consultees	Comments	Action
Appropriateness	Children's Cancer and Leukaemia Group Neuroblastoma Subgroup of the NCRI Children's Cancer and Leukaemia Clinical Study Group	Yes. Highly relevant to this population and timely, as agent is currently being assessed by EMA. An alternative, similar, product (Dinutuximab) has already received marketing authorisation	Comment noted.
	Neuroblastoma UK	Yes	
Wording	Neuroblastoma UK	Yes	
Timing Issues	Children's Cancer and Leukaemia Group Neuroblastoma Subgroup of the NCRI Children's Cancer and Leukaemia Clinical Study Group	Urgent - needs to be appraised as soon as possible. Once marketing authorisation is gained there will be considerable pressure to have this treatment available for children within the UK. At present antibody therapy is generally only available in the context of a clinical trial, but consideration needs to be given about how therapy will be made available within the NHS once marketing authorisation obtained.	Comment noted. NICE aims to issue guidance within 6 months after the technology receives its marketing authorisation.
	Neuroblastoma UK	Immunotherapy is currently only available to neuroblastoma patients enrolled in a relevant clinical trial. When the trial concludes it is unclear how the treatment will be made available to UK patients.	Comment noted.
Additional comments on the	Children's Cancer and Leukaemia Group	There are two forms of ch14.18 anti-GD2 monoclonal antibody that have been widely used clinically: ch14.18/	Comment noted.

Section	Consultees	Comments	Action
draft remit	Neuroblastoma Subgroup of the NCRI Children's Cancer and Leukaemia Clinical Study Group	SP2/0 (Dinutuximab, United Therpeutics) and ch14.18/CHO (Apeiron Biologics). These two antibodies are from the same original hybridoma clone, and have identical amino acid sequences, but have been grown in different producer cell lines (SP2/0 and CHO respectively). There are no clincal studies directly comparing the two agents, but as they are grown in different cell lines they are likely to have different glycosylation patterns which might signifiantly affect effector function. ch14.18 SP/20 (Dinutuximab) has been used in the North American Children's Oncology Group (COG) clinical trials, and ch14.18 /CHO has been used in the several European SIOPEN trials. In view of the potential functional differences between these agents, it should not be assumed that the clinical effects are the same, or that the benefit (if any) of combining antibody with cytokines (e.g. IL-2 and GM-CM-CSF) is equivalent. NICE has already undertaken a technology appraisal for Dinutuximab and it will be important for APN311 to be considered in this context, whilst recognising that there may be biological differences between these agents.	

Comment 2: the draft scope

Background information	Children's Cancer and Leukaemia Group Neuroblastoma Subgroup of the NCRI Children's Cancer and Leukaemia	Accurate. There remains a question about whether patients with relapsed neuroblastoma who have received anti-GD2 therapy as part of their front-line therapy can benefit from retreatment with anti-GD2 in the relapse setting	Comment noted. NICE guidance will only be issued in accordance with the marketing authorisation.

	Clinical Study Group		
	Neuroblastoma UK	Nothing additional to propose at this stage	Comment noted.
The technology/ intervention	Children's Cancer and Leukaemia Group Neuroblastoma Subgroup of the NCRI Children's Cancer and Leukaemia Clinical Study Group	The potential benefit (or otherwise) of giving anti-GD2 in combination with cytokines (such as IL2) needs to be considered and any comparison with Dinutuximab needs to take into account the fact that the pivotal study (Yu et al. NEJM) was of Dinutuximab in combination with IL-2 and GM-CSF; not antibody alone.	Comment noted. NICE guidance will only be issued in accordance with the marketing authorisation.
	Neuroblastoma UK	Yes	
Population	Neuroblastoma UK	Yes although the number of cases per annum in the UK is quoted as 90 whereas it is usually cited as c. 100; the URL in footnote 3 which is the source was not accessible at the time of compiling this response.	Comment noted. The link in footnote 3 has been updated and is accessible (accessed 28 January 2016).
Comparators	Children's Cancer and Leukaemia Group Neuroblastoma Subgroup of the NCRI Children's Cancer and Leukaemia Clinical Study Group	In the last 5 years (since the Yu et al study), anti-GD2 (ch14.18/SP2/0, ch14.18/CHO) has been viewed by clinicians in both Europe and US as part of the 'standard of care' for children with high risk neuroblastoma - such that the SIOPEN group did not feel it was acceptable to have a 'no antibody' arm in the HR-NBL-1 study. In the absence of availability of anti-GD2 antibody, isotretinoin would be considered standard of care in these patients.	Comment noted. At this stage, the scope should identify all potentially relevant comparators; identification of those comparators should be inclusive but should reflect established clinical practice in England. Care provided through a clinical trial cannot be considered to represent 'established clinical practice'.
	Neuroblastoma UK	Yes other than pointing out that the treatment is widely offered currently through a clinical trial, to the extent that I believe clinicians would not consider isotretinoin alone as a standard treatment.	Comment noted. At this stage, the scope should identify all potentially relevant comparators; identification of those comparators should be inclusive but should reflect established clinical practice in England. Care provided through a clinical trial cannot be considered to represent

			'established clinical practice'.
Outcomes	Children's Cancer and Leukaemia Group Neuroblastoma Subgroup of the NCRI Children's Cancer and Leukaemia Clinical Study Group	Yes - it is important to bear in mind that patients with HR neuroblastoma may have long-term health problems as a consequence of their intensive therapy that may impact on quality of life analyses	Comment noted.
	Neuroblastoma UK	Yes plus extended survival allows the possibility of further beneficial therapies becoming available	Comment noted.
Economic analysis	Children's Cancer and Leukaemia Group Neuroblastoma Subgroup of the NCRI Children's Cancer and Leukaemia Clinical Study Group	Economic analysis should take into account the very young age of this population, and the fact that addtional children cured with the therapy may potentially have a very long life expectancy. Additional survival time in a young child might be considered differently from an equal survivla benefit in a much older adult patient.	Comment noted. In line with the NICE Guide to the Methods of technology appraisal (section 5.1.15), the time horizon should be sufficient to reflect important cost and benefit differences between the technologies being compared.
	Neuroblastoma UK	If not covered in the childhood-specific criteria, consideration should be given to the point that a relatively short extension of life (e.g. 2-3 years) is more significant for children than for an adult population. In addition to NHS and Personal Social Services costs, consideration should be given to the cost impact on parents seeking to fund immunotherapy treatment overseas if it is not available in England and Wales.	Comment noted. The NICE Guide to the Methods of technology appraisal states that the perspective on outcomes should be all direct health effects, whether for patients or other people. The perspective adopted on costs should be that of the NHS and personal and social services (see section 5.1.7).
Equality	Children's Cancer and Leukaemia Group Neuroblastoma Subgroup of the NCRI Children's	As this is a very high cost drug, failure to achieve NICE approval would result in inequitable access to this therapy to children within UK. The question of how NHS patients	Comment noted.

	Cancer and Leukaemia Clinical Study Group	will obtain access to anti-GD2 immunotherapy once current (and planned) research studies close needs to be considered.	
Other considerations	Neuroblastoma UK	See comments above	
Innovation	Children's Cancer and Leukaemia Group Neuroblastoma Subgroup of the NCRI Children's Cancer and Leukaemia Clinical Study Group	Yes - introduction of immunotherapy has been a significant change to the management of high-risk neuroblastoma	Comment noted.
	Neuroblastoma UK	The use of immunotherapy has shown some promise in improving outcomes for children with this aggressive disease. As well as the data from clinical trials and associated publications, clinicians are developing new ways for the treatment to be administered which improve tolerance and may indicate further health gains.	Comment noted. The technology will be appraised in line with the administration methods specified in its marketing authorisation and Summary of Product Characteristics.
Questions for consultation	Neuroblastoma UK	Covered above	

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

Department of Health
Roche Products Ltd
Royal College of Pathologists