National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Dinutuximab for treating high-risk neuroblastoma

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

Comment 1: the draft remit

Section	Consultee/ Commentator	Comments	Action
Appropriateness	Neuroblastoma Children's Cancer Alliance UK	The NCCA UK believes it would be appropriate to refer this topic to NICE for approval.	Comment noted. No action required.
	National Cancer Research Institute & Children's Cancer and Leukaemia	Yes. Highly relevant to this population and timely, as agent is likely to receive EMA approval within next 12 months.	Comment noted. No action required.
	United Therapeutics	Yes, it is appropriate to refer this topic to NICE for appraisal.	Comment noted. No action required.
Wording	Neuroblastoma Children's Cancer Alliance UK	We agree with the wording.	Comment noted. No action required.
Wording (cont.)	United Therapeutics	United Therapeutics considers the wording of the draft remit to be appropriate.	Comment noted. No action required.

Section	Consultee/ Commentator	Comments	Action
Timing Issues	Neuroblastoma Children's Cancer Alliance UK	There is an urgent need for this drug to gain a UK marketing authorisation. There are currently no other treatments that are licenced in the UK that act to prevent relapse of neuroblastoma by immunotherapy. Patients urgently need access to this drug which has been effectively standard treatment in the US since 2009.	Comment noted. No action required.
	National Cancer Research Institute & Children's Cancer and Leukaemia	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	Comment noted. No action required.
	United Therapeutics	[redacted] High-risk neuroblastoma is associated with a significant unmet need and high mortality rate, and usually occurs in infants, children, and adolescents. There is no alternative licensed immunotherapy-based maintenance regimen for high-risk neuroblastoma. United Therapeutics requests that this topic be given a high priority, so that patients are able to access the improved survival benefit associated with dinutuximab as soon as the product gains marketing authorization.	Comment noted. No action required.

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Additional comments on the draft remit	National Cancer Research Institute & Children's Cancer and Leukaemia	There are two forms of ch14.18 anti-GD2 monoclonal antibody that have been widely used clinically: ch14.18/ SP2/0 (Dinutuximab, United Therapeutics) 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-CSF) is equivalent. In view of the fact that ch14.18 SP2/0 and ch14.18/CHO have been used in clinical trials for the same indications (high risk and relapsed neuroblastoma) in US and Europe respectively, and are both likely to receive marketing authorisation within the next 12-24 months, we strongly recommend that both are considered in the same NICE appriasal. However it is essential that the consultation recognises the potential biological differences between these agents.	Comment noted. The other anti-GD2 agent (ch14.18/CHO; Apeiron Biologics) will be considered through NICE's topic selection function. NICE aims to issue guidance within 6 months after the technology receives its marketing authorisation. Therefore, in order to issue timely guidance, this topic has been referred as an STA.
	United Therapeutics	No additional comments.	No action required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments	Action

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Background information	Neuroblastoma Children's Cancer Alliance UK	The incidence quoted in the document needs to be referenced, as it appears lower than is widely accepted. In addition, the incidence of 'high risk' neuroblastoma appears to be lower than is widely accepted for the UK. Additionally, the background information states that radiotherapy is given after surgery and before myeloablative therapy/stem cell transplant. This is usually not the case and radiotherapy is given after stem cell transplant. This has implication for the timing of the start of immunotherapy (dinutuximab).	Comment noted. The incidence of neuroblastoma is taken from the Cancer Research UK website (link). The clinical experts at the scoping workshop indicated that 'high risk' is not rigidly defined in clinical practice. This has been stated in the scope. The scope has been amended to state that radiotherapy may also be given after stem cell transplant.
	National Cancer Research Institute & Children's Cancer and Leukaemia	Accurate, but need to make reference to relapsed and refractory neuroblastoma. Children who relapse having not had anti-GD2 antibody as part of inital therapy may currently be offered anti-GD2 antibody therapy as part of their relapse therapy. The evidence for benefit in this scenaro, and indeed for primary refractory disease, should also be considered as part of this consultation	Comment noted. Scoping workshop attendees agreed that it would be appropriate to include people with relapsed disease and people with refractory disease as subgroups in the scope.

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	United Therapeutics	No comment.	No action required.
The technology/ intervention	Neuroblastoma Children's Cancer Alliance UK	The description is accurate.]	Comment noted. No action required.
	National Cancer Research Institute & Children's Cancer and Leukaemia	This combination of ch14.18/SP2/0 (dinutuximab) and cytokines (IL-2 and GM-CSF) was used in the NEJM Yu et al study, and has become the 'gold standard' in the US. However in Europe ch14.18/CHO (Aperion Biologics) has been given either alone or with IL-2. The current SIOPEN LTI and HR-NBL-1 studies are examing the benefit of giving IL-2 with ch14.18/CHO (preliminary data suggests this increases toxcity but may not improve outcome). GM-CSF(Sargramostim) is not currently marketed / available as a clinical reagent in Europe.	Comment noted. The availability of sargramostim in Europe is expected to be managed if dinutuximab receives a European marketing authorisation. No action required.
	United Therapeutics	Please note that Dinutuximab does not currently have a marketing authorisation in the UK for treating neuroblastoma, [redacted]	Comment noted. No action required.

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Population	Neuroblastoma Children's Cancer Alliance UK	While it is expected that those patients with a minimal evidence of disease or no evidence of disease would benefit most from dinutuximab, it is agreed that all patients who have completed stem cell transplant should be considered.	Comment noted. In appraisal of health technologies, NICE is bound by the marking authorisation of the technology being appraised. No action required.
	National Cancer Research Institute & Children's Cancer and Leukaemia	Should also include consideration of patients with relapsed and refractory disease.	Comment noted. Scoping workshop attendees agreed that it would be appropriate to include people with relapsed disease and people with refractory disease as subgroups in the scope.
	United Therapeutics	The population defined in the scope is appropriate. No subgroups have been identified for separate consideration.	Comment noted. Scoping workshop attendees agreed that it would be appropriate to include people with relapsed disease and people with refractory disease as subgroups in the scope.

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Comparators	Neuroblastoma Children's Cancer Alliance UK	It is not clear from the document that the current maintenance therapy (after stem cell transplant standard of care) for high risk neuroblastoma is isotretinoin only.	Comment noted. Scoping workshop attendees agreed to specify isotretinoin as the only comparator in the scope.
	National Cancer Research Institute & Children's Cancer and Leukaemia	In the last 5 years (since the Yu et al study), anti-GD2 antibody (ch14.18/SP2/0, ch14.18/CHO) has been viewed 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. Scoping workshop attendees agreed to specify isotretinoin as the only comparator in the scope.
	United Therapeutics	We believe the comparators listed in the draft scope to be inappropriate: there is no evidence to suggest management with isotretinoin, aldesleukin (interleukin-2), and sargramostim (granulocyte macrophage colony-stimulating factor) without dinutuximab would be an effective maintenance treatment for patients with high-risk neuroblastoma. There is evidence to suggest isotretinoin alone improves survival in high-risk neuroblastoma patients. Additionally, patients are not commonly treated with IL-2, GM-CSF, and isotretinoin in clinical practice. Standard of care in high-risk neuroblastoma is typically care provided through a clinical trial (if available) or isotretinoin alone (also known as "standard therapy"). Based on the available evidence, the appropriate comparator for the purposes of this appraisal would be isotretinoin alone.	Comment noted. Care provided through a clinical trial is not considered to represent 'established practice'. Scoping workshop attendees agreed to specify isotretinoin as the only comparator in the scope.

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Outcomes	Neuroblastoma Children's Cancer Alliance UK	The NCCA UK is of the opinion that dinutuximab prevents relapse, which is highly likely within two years of the end of current treatment. The treatment side effects can be severe but are manageable, and are without many of the long term side effects that are typical of high dose chemotherapy given to young children.	Comment noted. Scoping workshop attendees agreed that relapse prevention would be captured by progression-free survival, which is an outcome in the scope. No action required.
	National Cancer Research Institute & Children's Cancer and Leukaemia	Yes	Comment noted. No action required.
	United Therapeutics	Because the majority of neuroblastoma patients are aged less than 5 years, obtaining quality of life data through the EQ-5D or other standardized test was not feasible. Except for response rate and health-related quality of life, the outcome measures listed will appropriately capture the most relevant health benefits and harms of the technology. Response rate is not an appropriate outcome measure as patients in the maintenance treatment phase of neuroblastoma typically do not have measurable disease (maintenance therapy is designed to target minimal residual disease and to prevent relapse). Health-related quality of life was not assessed in the pivotal trials as the majority of the children treated were too young for an appropriate quality of life metric.	Response noted. Scoping workshop attendees agreed to remove response rate from the list of outcomes in the scope.

Section	Consultee/ Commentator	Comments	Action
Economic analysis	Neuroblastoma Children's Cancer Alliance UK	The time horizon should be lifetime.	Comment noted. No action required.
	National Cancer Research Institute & Children's Cancer and Leukaemia	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	Comment noted. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. No action required.
	United Therapeutics	A lifetime model would be appropriate for the economic analysis.	Comment noted. No action required.
Equality and Diversity	Neuroblastoma Children's Cancer Alliance UK	no comments	No action required.

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	National Cancer Research Institute & Children's Cancer and Leukaemia	As this is a very high cost drug, if it is shown to be clinically effective (and cost effective) failure to achieve NICE approval would result in inequitable access to this therapy to children within UK.	Comment noted. No action required.
	United Therapeutics	No comment.	Comment noted. No action required.
Innovation	Neuroblastoma Children's Cancer Alliance UK	This treatment is a step change in the treatment of neuroblastoma. Current treatments for high risk neuroblastoma are at the most intensive end of the cancer treatment spectrum, with a not insignificant number of those children treated dying from the treatment rather than the disease.	Comment noted. The company is encouraged to describe the innovative nature of dinutuximab-based therapy in their evidence submission. The Committee would normally consider this information during the course of the appraisal. No action required.

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	National Cancer Research Institute & Children's Cancer and Leukaemia	Yes - the Yu et al (NEJM 2010) COG study of ch14.18 /SP2/0 (dinutuximab), given with IL-2 and GM-CSF, did report a siginificant improvement in 2 year overall survival and event free survival for children with high risk neuroblastoma, and the results of this study triggered a 'step change' in the management of this population of children in both US and Europe.	Comment noted. The company is encouraged to describe the innovative nature of dinutuximab-based therapy in their evidence submission. The Committee would normally consider this information during the course of the appraisal. No action required.
	United Therapeutics	Dinutuximab will be the first licensed maintenance immunotherapy for high-risk neuroblastoma. Due to the significant overall and event-free survival benefits associated with its administration, dinutuximab represents an innovative therapy that is a step-change in the management of high-risk neuroblastoma. Based on the clinical trial data, the 2-year event-free survival for dinutuximab patients was 66% (compared to 46% with isotretinoin alone; P-value=0.01) and the 2-year overall survival was 86% (compared to 75% with isotretinoin alone; P-value=0.02). United Therapeutics believes all benefits from dinutuximab will be captured by the QALY calculation. The nature of the data available to account for dinutuximab's clinical benefit and safety is primarily found within two Phase 3 clinical trials. Additional unpublished evidence regarding long-term efficacy has been presented at major neuroblastoma conferences.	Comment noted. The company is encouraged to describe the innovative nature of dinutuximab-based therapy in their evidence submission. The Committee would normally consider this information during the course of the appraisal. No action required.

Section	Consultee/ Commentator	Comments	Action
Other considerations	Neuroblastoma Children's Cancer Alliance UK	It has become accepted by neuroblastoma specialists worldwide that anti-GD2 therapy should be standard of care for high risk neuroblastoma patients who have responded well to previous treatment. Currently many children access this type of therapy via various trials.	Comment noted. No action required.
	United Therapeutics	Dinutuximab is intended to be administered as indicated according to the marketing authorisation, in combination with GM-CSF, IL-2, and isotretinoin. Currently, GM-CSF is not approved for marketing authorization by the EMA for any indication. [redacted]	Comment noted. No action required.
Questions for consultation	Neuroblastoma Children's Cancer Alliance UK	High risk neuroblastoma is identified clinically by a variety of indicators. Currently all children identified as high risk in the UK will have a treatment plan at diagnosis that includes stem cell transplant.	Comment noted. The criteria used to define 'high risk neuroblastoma' have been amended in the scope.
	United Therapeutics	Due to the vague initial symptoms, neuroblastoma is often diagnosed late in the disease process. The initial diagnosis of neuroblastoma and risk category is determined through a variety of tests, including X-rays, CT scans, neurological exams, ultrasound, and/or bone marrow biopsy. High-risk patients are those that are greater than or equal to 18 months of age at diagnosis with metastatic disease or patients that have MYCN amplification.	Comment noted. The criteria used to define 'high risk neuroblastoma' have been amended in the scope.

Section	Consultee/ Commentator	Comments	Action
Additional comments on the draft scope	United Therapeutics	No additional comments.	No action required.

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

Department of Health

Royal College of Pathologists

Response to consultee and commentator comments on the provisional matrix of consultees and commentators (pre-referral)

Version of matrix of consultees and commentators reviewed: Provisional matrix of consultees and commentators sent for consultation					
Summary of comments, action taken, and justification of action:					
	Proposal:	Proposal made by:		Action taken: Removed/Added/Not included/Noted	Justification:
1.	Add Children with Cancer to matrix of consultees and commentators.	NICE Secretariat		Added	This organisation's interests are closely related to the appraisal topic and as per our inclusion criteria and equalities commitments. Therefore Children with Cancer has been added to the matrix under 'patient/carer' groups.

2.	Add British Paediatric Neurology Association (BPNA) to matrix of consultees and commentators.	NICE Secretariat		Added	This organisation has an area of interest closely related to this appraisal topic and meets the selection criteria to participate in this appraisal. The British Paediatric Neurology Association (BPNA) has been added to the matrix of consultees and commentators under 'professional groups'.
3.	Add Neuroblastoma Children's Cancer Alliance (NCCA UK) to matrix of consultees and commentators.	NCRI Children's Cancer Leukaemia CSG (with input from NCRI Children's Cancer Leukaemia CSG Neuroblastoma subgroup) and CCLG (with input from the CCLG Neuroblastoma Special Interest Group) NICE Secretariat		Added	This organisation has an area of interest directly related to this appraisal and meets the selection criteria to participate in this appraisal. The Neuroblastoma Children's Cancer Alliance has been added to the matrix of consultees and commentators under 'Relevant research' groups.

4.	Remove Children's Society from the matrix of consultees and commentators.	NICE Secretariat		Removed	This organisation's interests are not directly related to the appraisal topic and as per our inclusion criteria. The Children's Society has not been included in the matrix of consultees and commentators.
5.	Remove National Council for Palliative Care from matrix of consultees and commentators**.**	NICE Secretariat		Removed	This organisation's interests are not directly related to the appraisal topic and as per our inclusion criteria. The National Council for Palliative Care has not been included in the matrix of consultees and commentators.
6.	Remove National Parent Partnership Network from matrix of consultees and commentators.	Nice Secretariat		Removed	This organisation no longer exists and is currently known as Information Advice and Support Services Network (IASS) which is already included in the matrix of consultees and commentators.

7.	Remove Information Advice and Support Services Network (IASS) from matrix of consultees and commentators.	NICE Secretariat		Removed	This organisation's interests are not directly related to the appraisal topic and as per our inclusion criteria. The Information Advice and Support Services Network has not been included in the matrix of consultees and commentators.
8.	Remove Sue Ryder from matrix of consultees and commentators.	NICE Secretariat		Removed	This organisation's interests are not directly related to the appraisal topic and as per our inclusion criteria. Sue Ryder has not been included in the matrix of consultees and commentators.
9.	Remove WellChild from matrix of consultees and commentators.	NICE Secretariat		Removed	This organisation has declared that they no longer wish to participate in NICE appraisals. WellChild has not been included in the matrix of consultees and commentators.