National Institute for Health and Care Excellence

Health Technology Evaluation

Eflornithine for treating high-risk neuroblastoma with complete or partial response after immunotherapy ID4060
Response to stakeholder organisation comments on the draft remit and draft scope

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit and proposed process

Section	Stakeholder	Comments [sic]	Action
Appropriateness of an evaluation and proposed evaluation route	Norgine Pharmaceuticals Limited	This is an appropriate topic and evaluation route for NICE to consider.	Thank you for your comment.
	Solving Kids' Cancer UK	No comments.	Thank you for your comment.
Wording	Norgine Pharmaceuticals Limited	We would suggest a minor change in wording of the remit to acknowledge that the UK marketing authorisation for eflornithine is currently not finalised. The following wording is suggested: "To appraise the clinical and cost effectiveness of eflornithine within its anticipated marketing authorisation for treating high-risk neuroblastoma with complete or partial response after immunotherapy."	Thank you for your comment. The remit is intended to marketing authorisation at the point of final guidance, so no changes are needed. .

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	Solving Kids' Cancer UK	Yes.	Thank you for your comment.
Timing issues	Norgine Pharmaceuticals Limited	In children with high-risk neuroblastoma from a European cohort who have complete or partial response after immunotherapy, event-free survival is as low as 56% at three years post immunotherapy initiation.[1] There are no licensed treatment options available in the UK to improve these survival outcomes. Hence, it is important for NICE to provide a recommendation for the use of eflornithine after immunotherapy within the NHS as close to marketing authorisation approval as possible.	Thank you for your comment.
	Solving Kids' Cancer UK	Families are seeking to access this treatment abroad currently and to now access on compassionate access and/or named patient schemes.	Thank you for your comment.
Additional comments on the draft remit	Norgine Pharmaceuticals Limited	No additional comments	Thank you for your comment.
	Solving Kids' Cancer UK	None	Thank you for your comment.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Norgine Pharmaceuticals Limited	<u>Age at diagnosis</u> The draft scope states: "Neuroblastoma usually affects children under the age of 5 years." The company suggest expanding upon this source to note that	Thank you for your comments. The scope has been updated to

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		the median age of neuroblastoma diagnosis is 12-18 months[2], emphasising the very early burden of disease. Use of immunotherapy The draft scope states: "Standard of care in the maintenance phase is to treat for minimal residual disease with an immunotherapy-based regimen and isotretinoin". The company note that NICE TA538[3] specifically recommend dinutuximab beta for patients with at least partial response following consolidation therapy, and are not aware of any other appraisals or ongoing studies exploring alternative immunotherapy regimens. The technology The draft scope states: "It has been studied in single arm clinical trials in children, young people and adults with high-risk neuroblastoma with a complete or partial response to immunotherapy ***or high-risk neuroblastoma that is relapsed or refractory following partial or complete response to immunotherapy.***" Please note that the final portion of this sentence (in bold) is inaccurate; we would suggest rewording as follows to better reflect the relapsed/refractory population studied in NMTRC003/003b who are not required to have previously received immunotherapy: "…or high-risk neuroblastoma in patients with partial or complete response following previous relapse or refractory therapy".	specify dinutuximab beta and to include a median age at diagnosis. The technology section has been updated to better reflect the high-risk neuroblastoma population studied in the trial.
	Solving Kids' Cancer UK	Yes.	Thank you for your comment.
Population	Norgine Pharmaceuticals Limited	No comments	Thank you for your comment.

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	Solving Kids' Cancer UK	Yes. In the BeatCC clinical trials patients enrolled to receive DFMO had negative MIBG scans (no evidence of disease) or negative PET scans (no evidence of active disease), however PET scans are not routinely conducted for neuroblastoma and not part of established international neuroblastoma response criteria except for the subset of patients who are known to have MIBG negative disease.	Thank you for your comment.
Subgroups	Norgine Pharmaceuticals Limited	The company are not currently aware of any subgroups that should be considered separately.	Thank you for your comment.
	Solving Kids' Cancer UK	No.	Thank you for your comment.
Comparators	Norgine Pharmaceuticals Limited	According to guidelines relevant to high-risk neuroblastoma clinical practice in the UK,[4-6] there are currently no recommended or licensed treatment options for patients with complete or partial response following the induction, consolidation and maintenance immunotherapy. In light of this, the most appropriate comparator following immunotherapy will be routine monitoring.	Thank you for your comment. The comparators in the scope are intended to be broad, to capture the current management of the condition.
	Solving Kids' Cancer UK	Standard post-treatment follow-up / normal clinical management is appropriate comparator.	Thank you for your comment.
Outcomes	Norgine Pharmaceuticals Limited	The company agree that the most important health outcomes are captured.	Thank you for your comment.

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	Solving Kids' Cancer UK	Yes.	Thank you for your comment.
Equality	Norgine Pharmaceuticals Limited	There are no equality issues surrounding the use of eflornithine for the indicated patient population. Nevertheless, it must be noted that, as highlighted by the NICE Quality Standard QS55 and NICE Cancer Service Guideline CSG7, equity of treatment for children with cancer is a concern.[7,8] In addition, according to the Cancer Patient Experience Survey in 2010, people with rarer forms of cancer reported a poorer experience of their treatment and care than people with more common forms of cancer.[9] Therefore, access to a treatment such as eflornithine may help promote equality for both paediatric patients and those with rare forms of cancer. The intrinsic equality issues for medicines developed or licensed specifically in a paediatric population should also be considered: NHS England funding policy for medicines initially reimbursed in an adult population allow flexibility for extending funding to the paediatric population where there is evidence to support continued clinical effectiveness.[10] This extension policy requires no formal evaluation by NICE in the paediatric population for funding to be granted. Whilst this policy is very effective for expediting access to treatments for children and a great step towards efficiently serving these populations with high unmet need, it does highlight that it is an uneven field when it comes to treatment access in paediatric oncology and that there is a barrier to access for medicines indicated only for paediatric populations where full NICE appraisal is required; paediatric studies are often limited by reduced sample sizes and single arm design due to the unethical nature of conducting a placebo-controlled trial in children. These common features of paediatric specific studies lead to uncertainty during NICE appraisal, which is not necessarily present for adult indications. As a result, appraisal of medicines	Thank you for your comment. The committee will consider any relevant equality issues when it makes its recommendations.

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		indicated only in children may be subject to higher levels of scrutiny based on these intrinsic evidence gaps and challenges that come with the population, for which medicines granted extended paediatric funding by NHS England following prior reimbursement in adults are not affected by.	
	Solving Kids' Cancer UK	N/A	-
Other considerations	Norgine Pharmaceuticals Limited	No comments	Thank you for your comment.
	Solving Kids' Cancer UK	-	-
Questions for consultation	Norgine Pharmaceuticals Limited	**Where do you consider eflornithine will fit into the existing care pathway for high-risk neuroblastoma with complete or partial response after immunotherapy?** In alignment with current practice for prescription and monitoring of maintenance immunotherapy (dinutuximab beta) for patients with high-risk neuroblastoma in the UK, it is anticipated that eflornithine will fit into the pathway of care aligned to option C: Prescribed in secondary care with routine follow-up in secondary care. **For comparators and subsequent treatments, please detail if the setting for prescribing and routine follow-up differs from the intervention.**	Thank you for your comments.

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		As noted above, there are currently no recommended or licensed treatment options for patients with complete or partial response following induction, consolidation and maintenance immunotherapy. It is anticipated that the routine monitoring these patients would be subject to without eflornithine would also be conducted in the secondary care environment owing to the specialised nature of the disease and high rates of relapse. For subsequent treatment for patients' refractory to treatment or relapsed, it is expected that this will follow the treatment regimen used in the phase 2 randomised trial of topotecan and cyclophosphamide combination chemotherapy plus filgrastim.[11] This is aligned with the chemotherapy regimen applied for patients following treatment failure in the dinutuximab beta appraisal (TA538) and has been validated by clinical experts as the most common post immunotherapy treatment for relapsed patients. As above, it is anticipated that prescription and follow up associated with this treatment regimen is conducted in the secondary care environment. **Would eflornithine be a candidate for managed access?** No, in line with the decisions made around the applicability of a managed access agreement in the dinutuximab beta appraisal (TA538), it is unlikely that a managed access scheme would provide evidence of value to address any uncertainties within the submission. **Do you consider that the use of eflornithine can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?**	

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		Given the young age of the affected patients, it is likely that there is significant anxiety for the patients and their parents or carers. Eflornithine is able to improve the likelihood of long-term remission by preventing relapse, which will reduce anxiety for patients and improve the mental health of parents and carers. Additionally, eflornithine is an oral drug that is generally well tolerated by patients. Given the highly invasive and toxic nature of the preceding patient pathway, it is likely that use of eflornithine will be viewed positively by patients. Preventing disease relapse for patients will also support parents and carers in returning to normal life, including caring for other children and family members. Finally, it should be noted that due to the young age of the patient population, survival extrapolation will be required over a long duration. This extended extrapolation period will lead to uncertainty in the calculated QALY accrual, thus, may underestimate the benefit of treatment with eflornithine. **Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits.** No data was obtained during clinical trial. However, it is likely that patient and carer submissions will reflect this impact, as was reflected during TA538.	

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	Solving Kids' Cancer UK	-	-
Additional comments on the draft scope	Norgine Pharmaceuticals Limited	Remit: At the time of consultation, the marketing authorisation for eflornithine in the UK has not yet been granted. However, the wording in the scope accurately reflects the anticipated UK licence: "Eflornithine is indicated for treatment of high-risk neuroblastoma with complete or partial response after immunotherapy." Current or proposed marketing authorisation: Eflornithine (Vaniqa®) 11.5% cream is indicated for the treatment of facial hirsutism in women. At the time of consultation, the wording of the potential licensed indication has yet to be finalised. The expected wording of the licence is: [redacted] Regulatory process:	-

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		MHRA via the Project Orbis programme, Type C application. Target date for regulatory submission: [redacted] Anticipated date of CHMP positive opinion: Not applicable to UK procedural route. Anticipated date of EU regulatory approval: [redacted] Anticipated date of UK regulatory approval: [redacted] Anticipated date of UK launch: [redacted] The information around marketing authorisation including anticipated timelines is not currently in the public domain and is commercial in confidence.	

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		In line with NICE recommendations, modelling will be conducted in Microsoft Excel.	
	Solving Kids' Cancer UK	-	-

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

None