National Institute for Health and Care Excellence

HIGHLY SPECIALISED TECHNOLOGIES EVALUATION PROGRAMME

Response to consultee and commentator comments on the draft remit and draft scope

Ataluren for treating Duchenne muscular dystrophy with a nonsense mutation in the dystrophin gene (review of HST3) ID1642

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

Section	Consultee/ Commentator	Comments [sic]	Action
Wording	NHS England and NHS Improvement	Yes this reflects the issues correctly.	Thank you for your comment. No action required.
	Muscular Dystrophy UK	The wording is appropriate.	Thank you for your comment. No action required.
	PTC Therapeutics International Limited (manufacturer of ataluren)	Yes [wording is appropriate].	Thank you for your comment. No action required.
Timing Issues	Association of British	Duchenne muscular dystrophy is a progressive condition which leads to loss of ambulation in boys usually before their teenage years. There is a relatively	Thank you for your comment. NICE has

Section	Consultee/ Commentator	Comments [sic]	Action
	Neurologists (ABN)	limited time window therefore for children with this diagnosis already, to be treated with this drug. A lengthy process of appraisal would lead to a proportion of those children currently meeting the criteria for treatment, being no longer eligible by the time it is potentially approved.	scheduled this topic into its work programme. No changes to the remit required.
	NHS England and NHS Improvement	Not urgent.	Thank you for your comment. NICE has scheduled this topic into its work programme. No changes to the remit required.
	Muscular Dystrophy UK	With the Managed Access Agreement coming to an end in January 2023, there is an urgency to this evaluation to ensure people with Duchenne muscular dystrophy who could be eligible for this treatment if approved are able to continue having access it.	Thank you for your comment. NICE has scheduled this topic into its work programme and expects a decision to be made available prior to the end of the Managed Access Agreement. No changes to the remit required.
	PTC Therapeutics International Limited	Patients in England are currently receiving ataluren under a Managed Access Agreement (MAA) that will come to an end on 20 January 2023. Therefore, the NICE assessment must be completed prior to this date in order that patients currently receiving ataluren continue to receive their therapy.	Thank you for your comment. NICE has scheduled this topic into its work programme and expects a decision to be made available prior to

Section	Consultee/ Commentator	Comments [sic]	Action
			the end of the Managed Access Agreement. No changes to the remit required.
Additional comments on the draft remit	Muscular Dystrophy UK	No additional comments to add.	Thank you for your comment. No action required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	NHS England and NHS Improvement	This is complete and accurate.	Thank you for your comment. No action required.
	Muscular Dystrophy UK	This is accurate.	Thank you for your comment. No action required.
	PTC Therapeutics International Limited	No comments.	Thank you. No action required.
The technology/ intervention	NHS England and NHS Improvement	Yes [description of the technology is appropriate]	Thank you for your comment. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
	Muscular Dystrophy UK	Yes [description of the technology is appropriate]	Thank you for your comment. No action required.
	PTC Therapeutics International Limited	No comments.	Thank you. No action required.
Population	NHS England and NHS Improvement	Yes no additional sub-groups.	Thank you for your comment. No action required.
	Muscular Dystrophy UK	The population (people aged 2 years and older with Duchenne muscular dystrophy resulting from a nonsense mutation in the dystrophin gene who are able to walk) is defined appropriately. We do not feel that any groups should be considered separately.	Thank you for your comment. No action required.
	PTC Therapeutics International Limited	The population is appropriate. While we understand the need for a broad scope so that all evidence may be considered we would like to note that, as agreed with NICE and NHSE in November of 2020, the NICE re-evaluation is to make a recommendation regarding routine commissioning for ataluren-naive patients only.	Thank you for your comment. No action required.
Comparators	NHS England and NHS Improvement	Yes supportive care is the current clinical standard in the NHS. This is the best alternative.	Thank you for your comment. No action required.
	Muscular Dystrophy UK	The established clinical management without ataluren is an appropriate comparator.	Thank you for your comment. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
	PTC Therapeutics International Limited	We agree that the comparator should be 'established clinical management without ataluren' as described in the scope background and as outlined in the 2018 DMD Care Considerations	Thank you for your comment. No action required.
Outcomes	Association of British Neurologists (ABN)	The outcome measures listed are broad but all may not be relevant or measurable in a paediatric population e.g muscle strength. The Duchene population for whom this medication is intended are those who remain ambulant. Cardiac and respiratory function have usually not become adversely affected in this group as this will more commonly occur at a more advanced stage of the condition. These may not therefore be very informative outcomes.Validated measures of social/school engagement, mood and global function in children would be more relevant.	Thank you for your comment. Stakeholders can submit relevant for consideration. Some of the suggested outcomes may be captured under "health-related quality of life". The scope also refers to considerations beyond direct health benefits. The committee will consider the relevant outcomes. NICE is aware of the change to section 4.1 of the SmPC for ataluren, which removed the following statement from section 4.1 of the summary of product characteristics (SmPC): '*Efficacy has not been demonstrated in non-ambulatory patients*'.

Section	Consultee/ Commentator	Comments [sic]	Action
			Treatment stopping rules will be considered in this review, in line with the updated marketing authorisation and with clinical expert input. No further action required.
	NHS England and NHS Improvement	Yes [outcomes are appropriate].	Thank you for your comment. No further action required.
	Muscular Dystrophy UK	Yes, we were pleased to see time to wheelchair and number of falls included to properly capture the benefits of ataluren. We also would like to ensure that the mental health aspects within the health-related quality of life (for patients and carers) outcomes are explicitly reviewed.	Thank you for your comment. The committee will consider the relevant outcomes and the outcomes listed in the scope are not intended to be exhaustive. No further action required.
	PTC Therapeutics International Limited	The outcomes listed in the scope are appropriate. However, please note that there are limited clinical data available on the effect of ataluren on cardiac function and number of falls. There are no mortality data available from ataluren clinical studies, however mortality will be modelled in the cost-effectiveness model.	Thank you for your comment. No further action required.
Economic analysis	NHS England and NHS Improvement	No additional comments.	Thank you. No further action required.

Section	Consultee/ Commentator	Comments [sic]	Action
	PTC Therapeutics International Limited	The economic analysis will be in line with the NICE reference case. We propose a cost-utility analysis across a lifetime horizon to capture the incremental costs and QALYs accrued over patients' lives.	Thank you for your comment. No further action required.
Equality and Diversity	NHS England and NHS Improvement	No additional comments.	Thank you. No action required.
	Muscular Dystrophy UK	It is important to ensure that no patient has to travel excessive distances to receive the treatment given the level of disability that many will face.	Thank you for your comment. The committee will consider this potential equality issue. No action required.
	PTC Therapeutics International Limited	No comments.	Thank you. No action required.
Other considerations	NHS England and NHS Improvement	None.	Thank you. No action required.
	Genetic Alliance UK	If this technology is to be recommended, service delivery of Ataluren should be considered. For example, no patient should have to travel excessive distances to receive their treatment, especially as given the nature of the condition, mobility is significantly affected therefore making it more	Thank you for your comment. The committee will this potential equality

Section	Consultee/ Commentator	Comments [sic]	Action
		challenging. Additionally, plans to support healthcare professionals and service providers needs to be considered. It would be beneficial to see mental health support for patients and carers considered in this appraisal too.	issues. No action required.
	Muscular Dystrophy UK	Plans to support healthcare staff with the continued roll out of the treatment should be considered.	Thank you for your comment. The scope includes considerations of staffing and infrastructure requirements, including training and planning for expertise in the "*impact of the technology beyond direct health benefits"* section. No action required.
	PTC Therapeutics International Limited	No comments.	Thank you. No action required.
Innovation	Association of British Neurologists (ABN)	As an oral medication for this group it is certainly innovative as there is nothing else available.	Thank you for your comment. The committee will consider the innovative nature of ataluren. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
	NHS England and NHS Improvement	Yes this will represent a step change for these patients as standard of care is supportive.	Thank you for your comment. The committee will consider the innovative nature of ataluren. No action required.
	Muscular Dystrophy UK	Yes, if the data collected during the Managed Access Agreements shows the side effects are fewer and the efficacy greater than the current standard of care, then this would be a step change for this population.	Thank you for your comment. The committee will consider the innovative nature of ataluren. No action required.
	PTC Therapeutics International Limited	Ataluren is an innovative, first in class drug and is the first specific approved therapy for nmDMD that addresses the underlying cause of the disease. Prior to regulatory approval of ataluren for the treatment of nmDMD, the only management options for this devastating disease were supportive in nature and did not address the underlying cause of the condition i.e., the loss of functional dystrophin. Without functional dystrophin, muscles progressively weaken and deteriorate, leading to complete loss of ambulation, cardiac and pulmonary insufficiency, and finally death. Since ataluren received conditional approval from the EMA in 2014, no other treatments for the causal treatment of DMD have been approved by the EMA, highlighting the challenges of developing an effective treatment and conducting clinical trials in this condition. There have been a limited number of large, randomised studies in DMD and, through the ataluren trial programme, PTC Therapeutics are pioneering clinical trial research in this disease area. Despite the challenges of generating clinical evidence in areas of (ultra)-rare slowly progressing diseases, PTC has accumulated data on over 995 patients with nmDMD by	Thank you for your comment. The committee will consider the innovative nature of ataluren. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		conducting the largest clinical program in nmDMD to date[4-6] and developing the largest international nmDMD observational cohort for clinical effectiveness and safety (STRIDE Registry)[7,8]. The ataluren clinical studies have contributed a great deal of insight relating to the natural history of disease and use of clinically meaningful endpoints that will help to inform the design of future trials. In Phase 2 and 3 clinical studies (007 and 020), ataluren reduced the decline in 6MWD over 48 weeks compared with placebo, and consistently demonstrated benefit across multiple measures of muscle strength and function.[4,6] During the initial regulatory assessment in 2014, the EMA considered ataluren to offer therapeutic innovation and relevant benefits for a rare disease with high unmet medical need and this resulted in the early conditional approval of ataluren for the treatment of nmDMD ambulatory patients aged 5 years and older. Based on data from an additional study, in July 2018, an extension was granted to include ambulatory nmDMD patients aged 2 to less than 5 years old. The STRIDE (Strategic Targeting of Registries and International Database of Excellence) Registry is the first drug registry for patients with nmDMD and is the largest real-world study of patients with nmDMD to date. STRIDE provides data on patterns of ataluren use and long-term patient outcomes in real-world routine clinical practice. Ataluren treatment in STRIDE was associated with a delay in LoA by 5.4 years compared with matched natural history controls ($p<0.0001$).[9] Treatment with ataluren also delayed pulmonary function decline compared to natural history controls.[10] In clinical trials of patients with nmDMD, the observed safety profile of ataluren was overall comparable to that of placebo. Adverse reactions were generally mild or moderate and only one of 232 patients in the 2 randomised studies discontinued ataluren treatment due to an adverse reaction.[11]	

Section	Consultee/ Commentator	Comments [sic]	Action
		As such, the introduction of ataluren represented a step-change in management of nmDMD and has provided an effective treatment option for children in England with this life-threatening condition.	
Questions for consultation	Genetic Alliance UK	Will Ataluren have any potential health benefits that are unlikely to be fully captured in the QALY calculation? Do you foresee any potential barriers that would prevent the adoption of this technology into the UK health system?	Thank you for your comment. These questions will be addressed by the committee. No action required.
	Muscular Dystrophy UK	We recommend that the following questions are also addressed: Do you consider that the use of Ataluren can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation? Do you consider that there will be any barriers to adoption of this technology into practice?	Thank you for your comment. These questions will be addressed by the committee. No action required.
	PTC Therapeutics International Limited	There are no subgroups of people in whom ataluren is expected to provide greater clinical benefits or more value for money. All other questions for consultation have been addressed above.	Thank you for your comment. No action required.
	Association of British Neurologists (ABN)	There is no mention of whether stop criteria will be considered. This should be included.	Thank you for your comment. The committee will consider the evidence concerning stopping criteria. NICE is aware of the change to section 4.1 of the SmPC for

Section	Consultee/ Commentator	Comments [sic]	Action
			ataluren, which removed the following statement from section 4.1 of the summary of product characteristics (SmPC): '*Efficacy has not been demonstrated in non-ambulatory patients'*. Therefore, treatment stopping rules will be considered in this review, in line with the updated marketing authorisation and with clinical expert input. No action required.
Additional comments on the draft scope	Genetic Alliance UK	Given then expiry date for the managed access of Ataluren is in January 2023, we would like to emphasise the urgency of a final decision for Ataluren.	Thank you for your comment. NICE has scheduled this topic into its work programme and expects a decision to be made available prior to the end of the Managed Access Agreement. No changes to the remit required.
	Muscular Dystrophy UK	No additional comments to add.	Thank you. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
	PTC Therapeutics International Limited	It should be noted that whilst this assessment will incorporate results from the MAA in England, the submission will encompass the wider evidence collected over the five years since the previous assessment, including but not limited to, results of the STRIDE Registry.	Thank you for your comments. No action required.