

**NATIONAL INSTITUTE FOR HEALTH AND CARE
EXCELLENCE**

Addendum to Managed Access Agreement

**Ataluren for treating nonsense mutation
Duchenne muscular dystrophy (nmDMD) in
patients aged between 2 years and 5 years**

Date of Agreement	
NHS England Mr John Stewart, National Director of Specialised Commissioning, NHS England
PTC Therapeutics International Limited Mr Adrian Haigh, Director
Clinical Lead Professor Francesco Muntoni/Dr Adnan Manzur, ICH and GOSH, London
Patient Organisation(s) Catherine Woodhead, CEO MDUK Shelley Simmonds, CEO Action Duchenne
NICE Mr Meindert Boysen, Director of the Centre for Health Technology Evaluation, NICE

1 Purpose of and Background to Addendum Agreement

- 1.1 This Addendum to the Ataluren Managed Access Agreement has been drawn up by NHS England, PTC Therapeutics International Limited (the “Market Authorisation Holder” or “MAH”), and NICE, with patient community experts and clinicians. Any capitalised terms in this Addendum shall bear the same meaning as in the Ataluren Managed Access Agreement dated 20th July 2016 (the ‘MAA’).
- 1.2 On 23 July 2018, the European Commission issued a decision to extend the licensed therapeutic indication of Translarna to certain children aged 2 years and over with nmDMD. In light of this, the parties intend to expand the scope of treatment to children aged between 2 years and 5 years with nmDMD who fall within the expanded indication (the “Expanded Treatment Cohort”) in accordance with the terms of this Addendum.
- 1.3 Subject to Clause 1.6, this Addendum relates solely to the supply of the Expanded Treatment Cohort and is without prejudice to the treatment of patients outside the Expanded Treatment Cohort as provided for in the MAA (including Appendices 1 – 3 of the MAA).
- 1.4 This Addendum will allow the collection of safety and efficacy data on ataluren in order to inform clinical decisions regarding the best practice management of children aged between 2 years and 5 years with nmDMD.
- 1.5 For the avoidance of doubt, the parties intend this Addendum to be legally enforceable between them. The patient organisation(s) and clinician signatories will use their best endeavours to commend the Addendum to their patients and colleagues and encourage compliance with the Addendum.

1.6 A supplementary commercial in confidence ancillary agreement agreed between the licensed owner of ataluren (the MAH) and NHS England is appended to this Addendum at Appendix 2. This ancillary agreement amends the ancillary commercial agreement set out at Appendix 3 to the MAA in order to facilitate the supply of Translarna™ (ataluren) to the Expanded Treatment Cohort.

1.7 This Addendum includes the following:

- A statement that sets out the clinical criteria for starting and stopping treatment with ataluren.
- A set of efficacy parameters designed to allow review of performance of ataluren during the period of the Addendum

2 Commencement and period of agreement.

2.1 This Addendum shall take effect on 1st April 2019 and subject to clause 2.2 it will remain in force until the earlier of: (i) publication of a NICE HST of ataluren; or (ii) the expiry or termination of the MAA. The Guidance that NICE shall publish pursuant to clause 3.1 of the MAA shall take into account any data provided by the MAH about the Expanded Treatment Cohort in addition to the data provided pursuant to clause 3.1 of the MAA.

2.2 This Addendum shall terminate automatically on the termination or expiry of the confidential commercial agreement relating to the funding of ataluren for the Expanded Treatment Cohort, appended to Appendix 2 of this Addendum.

3 Patient eligibility

3.1 To receive treatment pursuant to this Addendum, patients must sign up to the 'Managed Access Patient Agreement' included in Appendix 1 to this Addendum, and NHS England and the MAH will use reasonable endeavors to ensure that this requirement (and the other

eligibility criteria specified in this clause 3) are reflected in their contracts with those clinical services providers who purchase ataluren. For the avoidance of doubt, references to the “Managed Access Agreement” in Appendix 1 are to be understood as references to this Addendum.

- 3.2 Under this Addendum, ataluren will be considered as a treatment option for all ambulatory patients aged between 2 years and 5 years with DMD resulting from a nonsense mutation (nmDMD). It will be added to existing standard treatment, including use of corticosteroids.
- 3.3 There may be patients, for example those with cognitive impairments, who are not able to complete a full set of tests at appointed visits. In such cases, clinicians will be expected to make all possible efforts to gather as much of the required data as possible.
- 3.4 Before receiving treatment pursuant to this Addendum, patients must be made aware of the start and stop criteria for receiving ataluren treatment:

Start criteria

- Patients must have a confirmed diagnosis of nonsense mutation DMD (nmDMD), which is the identified presence of an in-frame nonsense mutation in the dystrophin gene as determined by genetic testing (full sequencing). Each mutation will be confirmed as being amenable to treatment via committee, managed by the NorthStar lead, which will include a molecular geneticist and the MAH.
- Patients must be aged 2 years and over and able to crawl, stand with support or walk.
- Patients should only start once a full set of standard baseline specialist neuromuscular clinical and physiotherapy

assessments (including an initial blood test) have been obtained and once they have signed the Managed Access Patient Agreement (Appendix 1).

Stop Criteria

- The Patient is non-compliant with assessments for continued therapy (non-compliance is defined as fewer than two attendances for assessment in any 14-month period).

3.5 Patients who are taken off treatment will continue to be monitored and supported with normal best standard of care. These patients will continue to be assessed to allow gathering of important information regarding natural history of patients.

3.6 Patients are required to attend their clinics at least 2 times within a 14-month period for monitoring and dose adjustment

4 Data collection and monitoring

4.1 Data will be collected from all patients when they start ataluren treatment and at all subsequent clinic visits. Data will be entered into the NorthStar database.

4.2 Patients will be monitored according to the following criteria:

The NorthStar Ambulatory Assessment (NSAA) should be administered through the specialist centre. All parameters (17) will be attempted and if the patient is unable to carry out any parameter due to age and/or developmental stage, then this will be recorded as such. The NSAA will be attempted at each follow up visit and each score recorded.

4.3 Patients receiving ataluren will be monitored and data used to inform a further submission to the NICE HST by PTC.

4.4 The Child Health Utility 9D (CHU9D) quality of life measure will be collected twice per year from patients receiving ataluren.

4.5 In view of the importance of the impact of DMD on families and carers, the EQ-5D-5L will be measured in at least one caregiver of a child/young adult with DMD (e.g., parent). The results from this evaluation will be included within the re-submission.

5 Ownership of the data

5.1 By agreeing to take part in the MAA, the NorthStar Network will ask parents of patients to provide GDPR-compliant consent to have their children’s demographic and clinical data collected by their treating clinician. The data will be owned and controlled by the NorthStar Network but shared in anonymised form, as appropriate for the requirements of the MAA whilst respecting patient confidentiality, with the MAH, NHS England, and NICE for the purpose of assessing the benefit of treatment. The MAH will be responsible for the timely analysis of the data and submitting the relevant reassessment report to NICE during the fifth year of this MAA.

5.2 The data will be collected by the clinicians at the NorthStar expert centres.

5.3 All data collected pursuant to this Addendum shall be stored and processed in accordance with all applicable data protection laws.

6 Funding

6.1 The treatment provided for under this Addendum will be funded by NHS England from the start of this Addendum.

6.2 [REDACTED]

7 Exit strategy

7.1 If at the termination or expiry of this Addendum: (i) NICE does not recommend ataluren for NHS funding for patients who form part of the Expanded Treatment Cohort, NHS England funding for ataluren will cease to be available and treatment will cease (in which case cessation shall be managed between the MAH and NHS England to ensure it is effected in a controlled manner); or (ii) NICE recommends ataluren for NHS funding, further funding from NHS England will not be automatic and will be conditional on the agreement of commercial terms in relation to such funding between NHS England and the MAH.

7.2 The cessation of funding and the conditionality of further funding as specified in clause 7.1 above apply notwithstanding any desire which patients and their NHS clinicians may have for continued treatment with ataluren. NHS England and the MAH shall use their reasonable endeavours to ensure that any patient being treated with ataluren which is funded by NHS England under the terms of this Addendum is made aware of these funding limitations and accepts them when they sign the Patient Agreement (Appendix 1).

8 Counterparts

8.1 This Addendum may be executed in any number of counterparts, each of which when executed and delivered shall constitute a duplicate original, but all the counterparts together shall constitute one agreement.

8.2 Transmission of the executed signature page of a counterpart of this Addendum by (a) fax or (b) email (in PDF, JPEG or other agreed format) shall take effect as delivery of an executed counterpart of this Addendum. If either method of delivery is adopted, without prejudice to the validity of the Addendum thus made, each party shall

provide the others with the original of such counterpart as soon as reasonably possible thereafter.

- 8.3 No counterpart shall be effective until each party has executed and delivered at least one counterpart.

Signed by	NHS England
Signed by	Company
Signed by	Clinical Expert
Signed by	NICE
Signed by	Patient Organisations (MDUK & AD)

Appendix 1

Ataluren (Translarna™) for nonsense mutation Duchenne muscular dystrophy (nmDMD) Managed Access Patient Agreement

NICE have approved reimbursement of ataluren, licensed as Translarna™, subject to a number of measures that will be used to assess the compliance to a Managed Access Agreement (MAA)¹ in England and to ensure that all relevant stakeholders have a common understanding that such measures have the agreement and backing of all involved and will therefore be implemented.

The NICE MAA includes: -

- The clinical criteria for starting and stopping treatment with ataluren.
- Agreement that patient information will be collected and included into the NorthStar database in order to monitor patients' responses to ataluren treatment.
- Agreement between the MAH and NHS England, which is in addition to the patient access scheme, in order to manage financial risk for NHS England.

1. Patient Eligibility

The clinical community and patient organisations feel it is appropriate and right that all patients diagnosed with Duchenne muscular dystrophy (DMD) resulting from a nonsense mutation who are aged 2 years and over and who are ambulatory should have access to ataluren (Translarna™) in England.

Ataluren will be added to existing standard treatment, including use of corticosteroids.

Patients must be made aware of the start and stop criteria for receiving ataluren treatment and are required to attend their clinics 2 times for assessment within a 14-month period.

All patients will sign up to the 'Managed Access Patient Agreement'.

2. Access to treatment and data collection

The start criteria in this MAA have been used because they form the basis upon which the European licence for Translarna™ (ataluren) was granted.

¹ Addendum to Managed Access Agreement: ataluren for treating nonsense mutation Duchenne muscular dystrophy (nmDMD), dated 20 July 2016.

3. Start Criteria

- Patients must have a confirmed diagnosis of Duchenne muscular dystrophy resulting from an in-frame nonsense mutation in the dystrophin gene. The presence of a nonsense mutation in the dystrophin gene should be determined by genetic testing.
- Patients must be aged 2 years and older and able to crawl, stand with support or walk.
- Patients should only start once a full set of standard baseline specialist neuromuscular clinical and physiotherapy assessments (including an initial blood test) have been obtained.
- Patients / parents will be expected to attend their clinic 2 times a year for assessment within a 14-month period.

4. Stop Criteria

Patients will become ineligible for further treatment where:-

- The patient is non-compliant with assessments for continued therapy where non-compliance is defined as fulfilling fewer than 2 attendances for assessment within any 14-month period.
- Patients who are taken off treatment will continue to be monitored for disease deterioration and supported with other clinical measures. These patients should continue to be assessed to allow gathering of important information.

The MAA (and therefore agreed funding for ataluren) expires 5 years after NICE's recommendations being published in 2016 or following a further review should this be sooner. After year four, a comprehensive review will look at the benefits of ataluren. Any funding beyond such 5-year term will be conditional on NHS England agreeing the terms of such funding with PTC, the manufacturer of ataluren.

Accordingly, there are currently no arrangements to enable access to ataluren to be available as part of standard NHS care following the expiry of the MAA. Any continued access to ataluren beyond this point will be subject to consideration by NICE and publication of further recommendations. If NICE does not recommend ataluren in its further review at that time patients will discontinue NHS treatment with ataluren.

Appendix 1

Ataluren (Translarna™) for nonsense mutation Duchenne muscular dystrophy (nmDMD) Managed Access Patient Agreement

If you feel that you and/or your child will be able to comply with the above, please fill in your details below and sign for reimbursed treatment to begin.

Patient Name: _____

Parent/Carer Name: _____

Parent/Carer Signature: _____

Date: _____

Name of Clinician: _____

Signature of Clinician: _____

Date: _____

Appendix 2

**Ancillary Agreement between PTC Therapeutics International Limited
and NHS England**

*(This ancillary agreement contains commercial-in-confidence information and
has been redacted from the Addendum to the Managed Access Agreement).*