BÄSTA LIVSPLATSEN
Region Halland

Beslut – Ordnat införande

Datum
2018-02-21

Diarienummer
RS180142

Regionkontoret
Hälso- och sjukvård, Avdelningen för kunskap
Magnus Bengtsson
Läkemedelsstrateg

Tf Regiondirektör

Ordnat införande av Translarna (ataluren) vid Duchennes muskeldystrofi

Förslag till beslut från Region Hallands prioriterings- och evidensråd

Införande enligt NT-rådets rekommendation:

- Att avstå från nyinsättning av Translarna till dess att en hälsoekonomisk värdering från TLV finns tillgänglig.
- Att patienter som ingått i de kliniska studier som avslutades under hösten 2016 kan få fortsatt behandling inom godkänd indikation under noggrann uppföljning.
- I de fall där behandling inleds ska de kriterier för när behandlingen ska avbrytas ("stoppkriterier") som preciserats i NICE Managed Access Agreement användas
  - Patienten har förlorat all gångförmåga på grund av sjukdomstillståndet och har inte förmåga att stå utan stöd. I sådana fall sätts behandlingen ut inom 6 månader efter att patienten förlorat all gångförmåga.
  - Patienten kan på grund av compliance-problem eller av andra skäl inte följa planerad behandling och uppföljning på ett sådant sätt att säker nytta av behandlingen kan visas.
- I de fall där behandling blir aktuell ska ansökan om individuell subvention (rekvisitionsundantag) lämnas in till Regionkontorets läkemedelsfunktion.

Bakgrund

Godkänd indikation aktuell för ordnat införande

Translarna är indicerat för behandling av Duchennes muskeldystrofi, som orsakas av en nonsensmutation i dystrofingenen, hos rörliga patienter 5 år och äldre. Effekten har inte påvisats hos icke-rörliga patienter.

Motivering för ordnat införande

Enligt Helsingforsdeklarationen finns ett ansvar för fortsatt behandling av patienter som deltagit i kliniska studier. NT-rådet har därför uppdaterat sin tidigare rekommen-

dation som var att avstå behandling med ett undantag för behandling av de patienter som ingått i de kliniska studierna som avslutades hösten 2016 och som har objektiv nytta av behandlingen.

I Region Halland är det aktuellt med sådant undantag.

Sjukdomens svårighetsgrad

Inte definierad.

Åtgärdens effektstorlek

Effekterna av läkemedelet bedöms fortfarande som osäkra.

Sjukdomens sällsynthet

Inte definierad.

Kostnadseffektivitet

Inte bedömd.

Förmånsbeslut - TLV

Finns inget beslut.

Sidoavtal

Nationellt avtal har förhandlats fram och är tecknat av Region Halland för perioden 2017-10-01 – 2019-03-31.

Avtal endast tillgängligt att teckna för de landsting med patienter som tidigare behandlats i kliniska studier. Avtalet är konstruerat på sådant sätt att läkemedlet måste rekvireras och delas ut till patient från vårdenhet.

Återbäring hanteras av respektive landsting kvartalsvis i efterskott.

Regionala expertgruppsutlåtande

Inget regionalt utlåtande finns.

Konsekvensanalys

Ekonomiska konsekvenser

Halland har patientunderlag som tidigare ingått i klinisk studie. Beräknad årskostnad för behandling är 5,6 Mkr. Det finns en stor osäkerhet när det gäller behandlingens längd och kostnaden kvarstår tillsvidare.

Kostnaden är beräknad på listpriset för Translarna vilket innebär att de redovisade kostnaderna är innan nationell riskdelning. Faktisk kostnad blir betydligt lägre.

Med den finansieringslösning som är en del av beslutet, individuell subvention (rekvisitionsundantag) kommer behandling med Translarna finansieras genom den centrala budgeten.

Det finns ingen alternativ läkemedelsbehandling och därför ingen relevant alternativkostnad.

Organisatoriska konsekvenser

Inga identifierade.

Behov av utbildning

Inget identifierat.

Implementeringsplan

Införandeprocess

Nationell rekommendation finns framtaget för Translarna. Denna och Nice Managed Access Agreement ska följas absolut.

Kommunikationsplan

Beslut kommer att publiceras på Region Hallands webbsida för ordnat införande.

Uppföljningsplan

Användningen av Translarna följs regionalt av läkemedelsverksamheten på Regionkontoret. Återkoppling lämnas vid behov till rekvirerande enheter.

Livslängd

Beslutet om ordnat införande granskas och revideras senast 24 månader efter beslut eller vid nytt beslut från TLV, NT-rådet eller Läkemedelsverket.

Beslut enligt förslag från Region Hallands Prioriterings och evidensråd

Halmstad 27/2 -18
.....
(Ort och datum)

.....
Jörgen Preuss

Tf Regiondirektör

Bilagor:

Yttrande från NT-rådet.

NICE Managed Access Agreement

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Managed Access Agreement

Ataluren for treating nonsense mutation Duchenne muscular dystrophy (nmDMD)

Date of Agreement	
NHS England	…… Dr Jonathan Fielden - Director of Specialised Commissioning Deputy National Medical Director NHS England
PTC Therapeutics International	…… Mr Adrian Haigh - Director
Clinical Lead	…… Professor Francesco Muntoni/Dr Adnan Manzur, ICH and GOSH, London
Patient Organisation(s)	…… Mr Robert Meadowcroft, CEO MDUK …….. Ms Diana Ribeiro, CEO Action Duchenne
NICE	…… Professor Carole Longson / Sir Andrew Dillon

1 Purpose of agreement

1.1 The objectives of the document as a whole are to embody a set of auditable measures that will be used to support concerns raised by

the NICE Committee in their evaluation; communicated in the second consultation document and final guidance.

1.2 This Managed Access Agreement has been drawn up by NHS England, PTC Therapeutics International (the "Market Authorisation Holder" or "MAH"), and NICE with the engagement of patient community experts and clinicians.

1.3 For the avoidance of doubt, the parties intend this Managed Access Agreement to be legally enforceable between them. The patient organisation(s) and clinician signatories will use their best endeavours to commend the Agreement to their patients and colleagues and encourage compliance with the Agreement.

1.4 A Commercial in confidence ancillary agreement containing certain terms relating to the supply of Translarna™ (ataluren) agreed between the licensed owner of ataluren (PTC Therapeutics International) and NHS England is appended to this Agreement at Appendix 3).

2 Background

2.1 The NICE evaluation has developed positive recommendations conditional on a Managed Access Agreement (MAA) being developed and agreed by key stakeholders in the use of ataluren in the NHS in England.

2.2 This MAA includes the following:

- A statement that sets out the clinical criteria for starting and stopping treatment with ataluren.
- A cohort management plan to evaluate the performance of ataluren over the 5 years of the MAA
- Agreement between the MAH and NHS England to manage financial risk.

3 Commencement and period of agreement.

3.1 This MAA shall take effect on the date of publication of the Guidance. Subject to clause 3.2, it will remain in force until the earlier of: (i) publication of a NICE HST of ataluren or; (ii) a maximum of 5 years. For the avoidance of doubt, this MAA shall expire automatically on the 5th anniversary of its term if it has not expired earlier as a result of the publication of a NICE HST of ataluren. The MAH will provide the relevant data required for the review of the guidance on the product performance after the fourth year of this MAA. NICE will reissue guidance to the NHS in England based on a review of the data during the fifth year of this MAA. For the purposes of this clause, "Guidance" means the guidance expected to be published by the National Institute for Health and Care Excellence in 2016 in relation to the use of ataluren.

3.2 This MAA shall terminate automatically on the termination or expiry of the commercial agreement relating to the funding of ataluren and entered into between PTC Therapeutics and NHS England.

4 Patient eligibility

4.1 To receive treatment, patients must sign up to the 'Managed Access Patient Agreement' included in Appendix 2 to this MAA, and NHS England and the MAH will use reasonable endeavours to ensure that this requirement (and the other eligibility criteria specified in this clause 4) are reflected in their contracts with those clinical services providers who purchase ataluren.

4.2 Ataluren will be considered as a treatment option for all ambulatory patients aged 5 years and older with DMD resulting from a nonsense mutation (nmDMD). It will be added to existing standard treatment, including use of corticosteroids.

4.3 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.

4.4 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).
- Patients must be aged 5 years and older and able to walk 10 steps unaided.
- Patients should only start once a full set of standard baseline criteria has been obtained and once they have signed the Managed Access Patient Agreement (Appendix 2).

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).
- If a patient has lost all ambulation (i.e. can no longer stand even with support) and has become entirely dependent on wheelchair use for all indoor and outdoor mobility (other than for reasons of an accident and/or an intercurrent illness), the patient's physician needs to discuss stopping ataluren treatment.
    - In such cases as defined above, patients should stop treatment no later than 6 months after becoming fully non-ambulant.

4.5 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 non-ambulatory patients.

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

5 Data collection and monitoring

5.1 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.

5.2 Patients will be monitored according to the standard NorthStar criteria (see Appendix 1).

5.3 Patients receiving ataluren will be compared to an historical natural history population as well as a matched control group in order to assess response to treatment over the 5 year period of the MAA. The historical data and matched control group will be identified from patients included in the NorthStar registry.

5.4 The matched control group will comprise 100 DMD patients having the same age (+/- 6 months) and linearised NSAA (LNSAA) score (+/-1) as a cohort of 50 patients starting ataluren treatment within 3 months of the commencement of the MAA; patients will also be matched for steroid regimen. After the 50th ataluren patient has been included into the MAA, further patients starting commercial ataluren therapy will be monitored but will not form part of the formal MAA treatment cohort.

5.5 The matched control group will be receiving best standard of care (BSC) but will not be receiving any disease modifying therapies. In the case of a matched control patient starting treatment with a disease modifying therapy – either commercially or through a

clinical trial – they will be removed from any analyses comparing their data with the ataluren-treated cohort.

5.6 In line with the Statistical Analysis Plan (SAP; Appendix 4) after 2 years of observation for the entire cohort i.e. once the last patient starting commercial ataluren within the MAA cohort has completed 2 years of treatment, the LNSAA score for the ataluren treated cohort will be compared to the matched controls and to the historical natural history data and any difference vs expectation will be taken into consideration for the full analysis. In order to submit the data within the 5 year MAA period, the results will need to be analysed after the cohort has completed 4 years of ataluren treatment. Details of the SAP are included in Appendix 4.

5.7 Using similar extrapolations to those seen in study 020, as well as the natural history data as published by Ricotti (Ricotti et al, 2015), and considering the composition of the cohort to be similar to study 020, the cohort of patients receiving ataluren is expected to have a decline over the initial 2 years of the MAA by [redacted] linearized points on the NSAA scale, a numeric difference of around [redacted] points from the matched control cohort which is expected to have declined by [redacted] points over the same period. The analysis will take account of the natural history of Duchenne muscular dystrophy, which is for an increase in performance (and hence LNSAA score) up to the age of about 7 years, followed by decline.

5.8 An evaluation will be made at 2 years in order to compare the ataluren and matched control group declines and to then confirm or recalibrate the extrapolation at 4 years so as to provide data to submit for the 5 year renewal.

5.9 Because of the size of the sample, length of observation and variability [redacted] at year 2 to be demonstrated. As stated in section 5.8, the results at year 2 will serve as a validation/calibration of the

expectations and parameters of performance for year 4 where we expect to be able to confirm ataluren's performance as modelled.

5.10 A priori, the analysis at year 4 will be done by comparing the difference in the [redacted] for ataluren patients and the matched controls between baseline and the 4th year observation.

5.11 The Child Health Utility 9D (CHU9D) quality of life measure will be collected twice per year from patients receiving ataluren, and from matched controls, who consent.

5.12 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 4 year re-submission.

5.13 In addition to the results from the MAA, all other available data on ataluren, including from ongoing studies, will be used to inform the submission to NICE for the updated guidance.

6 Ownership of the data

6.1 By agreeing to take part in the MAA patients will be asked to consent to have their demographic and clinical data collected by their treating clinician. The data will be owned by the NorthStar Network but shared, 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 the 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.

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

7 Funding

7.1 The treatment will be funded by NHS England from the start of this MAA.

7.2 The MAH has registered a confidential patient access price with the Department of Health, and has agreed further commercial arrangements with NHS England, to respond to the NICE committee's concerns. These confidential arrangements, set out in the ancillary agreement (Appendix 3), apply for the duration of the MAA.

8 Ongoing Review of this Agreement

8.1 A body of NHS England, the MAH, clinical experts and patient organization representatives will meet annually to consider how this agreement is working. They will meet under the chairmanship of NICE.

9 Exit strategy

9.1 If at the end of the 5 year MAA: (i) NICE does not recommend ataluren for NHS funding, NHS England funding for ataluren will cease to be available for all patients 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); (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.

9.2 The cessation of funding under this MAA and the conditionality of further funding as specified in clause 9.1 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 this MAA is made aware of these funding limitations and accepts them when they sign the Patient Agreement (Appendix 2).

10 Counterparts

10.1 This Agreement 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.

10.2 Transmission of the executed signature page of a counterpart of this Agreement by (a) fax or (b) email (in PDF, JPEG or other agreed format) shall take effect as delivery of an executed counterpart of this Agreement. If either method of delivery is adopted, without prejudice to the validity of the agreement thus made, each Party shall provide the others with the original of such counterpart as soon as reasonably possible thereafter.

10.3 No counterpart shall be effective until each Party has executed and delivered at least one counterpart.

Signed by	**Director Specialised Commissioning, NHS England**
Signed by	**Company**
Signed by	**Clinical Expert**
Signed by	**NICE**
Signed by	**Patient Organisations (MDUK & AD)**

Appendix 1

NorthStar protocol for clinic evaluations

See following attachments:

Attachment A: NorthStar – Key Medical Information
Attachment B: NorthStar – Medical Assessment
Attachment C: NorthStar – Physiotherapy Assessment

Appendix 2

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) 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 5 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.

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 5 years and older and able to walk 10 steps unaided

- Patients should only start once a full set of standard baseline criteria has 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.

- The patient has lost all ambulation and has become entirely dependent on wheelchair use for all indoor and outdoor mobility (other than for reasons of an accident and/or an intercurrent illness). In such cases patients will stop treatment no later than 6 months after becoming fully non-ambulant.

- 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. At 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 2

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 3

Ancillary Agreement between PTC Therapeutics and NHS England
(The ancillary agreement contains commercial-in-confidence information and has been redacted from the managed access agreement)

Appendix 4

Statistical Analysis Plan
for
Managed Access Agreement
Ataluren for treating nonsense mutation Duchenne muscular dystrophy (nmDMD)

(The statistical analysis plan contains commercial-in-confidence information and has been redacted from the managed access agreement)