Pwyllgor Gwasanaethau Iechyd Arbenigol Cymru (PGIAC)
Welsh Health Specialised Services Committee (WHSSC)

Specialised Services Policy: CP118
Ataluren for treating Duchenne muscular dystrophy with a nonsense mutation in the dystrophin gene

Document Author:	Specialised Planner for Neurosciences
Executive Lead:	Acting Director of Planning
Approved by:	Management Group
Issue Date:	01 September 2016
Review Date:	September 2019
Document No:	CP118

Document History

Revision History			
Version No.	Revision date	Summary of Changes	Updated to version no.:
		NICE Managed Access Agreement transferred to WHSSC agreed format	0.1
Date of next revision			

Consultation		
Name	Date of Issue	Version Number
NICE Managed Access Agreement	20/07/16	
Corporate Directors Group	15/08/16	0.1
Management Group	25/08/2016	

Approvals		
Name	Date of Issue	Version No.
Management Group	25/08/2016	1.0

Distribution – *this document has been distributed to*			
Name	By	Date of Issue	Version No.

Policy Statement

Background	On 20th July 2016 NICE recommended the use of Ataluren for Duchenne Muscular Dystrophy with a nonsense mutation in the dystrophin gene. This was approved through the NICE HST process and has been endorsed by AWSMG. The NICE guidance is due to be reviewed in July 2020. Duchenne muscular dystrophy (DMD) is a severe, progressive X-linked recessive disorder that mainly affects males. A nonsense mutation causes a single-point alteration in deoxyribonucleic acid (DNA), which results in the presence of a premature stop codon in the protein-coding region of the corresponding messenger ribonucleic acid (mRNA). This premature stop codon causes the production of a shortened protein and leads to loss of dystrophin protein function and consequently to disease. Patients with DMD have a continual and relentless decline in physical function followed by a decline in respiratory and cardiac function. They develop progressive muscle weakness from early childhood, losing lower and then upper body function. This loss of physical function continues to progress and wheelchair use is normally required from around 12 years of age. Full loss of physical function occurs from around age 20 years and patients become dependent on carers for all aspects of living, including feeding and personal care. Loss of walking ability (ambulation) in patients with DMD is a key milestone; this impacts quality of life significantly and is correlated with a faster rate of deterioration of other major clinical outcomes such as loss of upper-limb mobility and loss of self-feeding, as well as the need for breathing assistance. The subsequent cardiac and respiratory complications of DMD usually lead to death in early adult life (usually by age 30). There is no current therapy for DMD that treats the underlying cause of the disease. Current management of DMD includes treatment with corticosteroids, which temporarily increase muscle strength and function but can also have significant side effects. Other interventions include cardiac and respiratory monitoring and support, occasional inpatient orthopaedic intervention, spinal surgery and rehabilitation. Ataluren restores the synthesis of dystrophin by allowing ribosomes to read through premature stop codons that cause incomplete dystrophin synthesis in nonsense mutation Duchenne muscular dystrophy (DMD), thus targeting the cause of the disease.

Summary of Access 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.
Responsibilities	Referring physicians should: • Inform the patient that this treatment is not funded outside the criteria in this policy and • Refer via the agreed pathway Clinician considering treatment should: • Discuss all the alternative treatment with the patient; • Advise the patient of any side effects and risks of the potential treatment; • Inform the patient that treatment is not funded outside of the criteria in the policy

Table of Contents

1. Aim

1.1 Introduction

The use of Ataluren for Duchenne Muscular Dystrophy has been approved through the NICE HST process as of July 2016. This document outlines the policy for the use of Ataluren for the treatment of Duchenne Muscular Dystrophy (DMD). The policy has been based on the established NICE Managed Access Agreement. The policy applies to residents of all seven Health Boards in Wales.

The purpose of this document is to:

- Specify the clinical circumstances under which patients will be able to access Ataluren for DMD;
- Clarify the start and stop criteria for this treatment;
- Outline the referral process; and
- Define the quality and outcome measures

In creating this policy, WHSSC has considered the evidence base for clinical and cost effectiveness, the assessment made by All Wales Medicine Strategy Group and the Ministerial decision on options for treatment.

1.2 Relationship with other Policies and Service Specifications

This document should be read in conjunction with the following documents:

- All Wales Policy: Making Decisions on Individual Patient Funding Requests (IPFR).

2. SCOPE

2.1 Definition

Duchenne Muscular Dystrophy (DMD) is a severe, progressive X-linked recessive disorder that mainly affects males. DMD with a nonsense mutation is caused by a single base variation in a person's DNA, which leads to incomplete dystrophin production in the skeletal, smooth and cardiac muscle fibres. Dystrophin production is usually affected from birth and symptoms of DMD appear by age 3 years. The main symptom of DMD is motor dysfunction but, as the disease progresses, the gastrointestinal tract and vital organs such as the heart are affected. People with DMD have a decline in physical functioning, with subsequent respiratory and cardiac failure that leads to death, usually before age 30 years.

Ataluren (Translarna™) is a drug specifically used to treat nonsense mutation DMD. Ataluren allows the ribosomes to read through the premature stop

codon, whilst respecting the normal stop codon, to restore the synthesis of functional dystrophin protein.

Six-minute walk distance (6MWD) measures the distance an individual is able to walk over a total of six minutes on a hard, flat surface. The goal is for the individual to walk as far as possible in six minutes. The individual is allowed to self-pace and rest as needed as they traverse back and forth along a marked walkway.

LNSAA (Linearised NorthStar Ambulatory Assessment) is a validated unidimensional functional scale for ambulant boys with DMD.

Child Health Utility 9D (CHU9D)

EQ-5D-5L (EuroQol – 5 Dimensions – 5 Levels) is a quality of life questionnaire. It comprises five dimensions of health: mobility, ability to self-care, ability to undertake usual activities, pain and discomfort, and anxiety and depression.

2.2 Codes

ICD-10 Codes

Code Category	Code	Description
	G71.0	Duchenne Muscular Dystrophy

3. ACCESS CRITERIA

3.1 Criteria for Treatment

To receive treatment, patients, parents or guardians must sign up to the 'Managed Access Agreement' (MAA).

3.2 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.

3.3 Stop criteria

- 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.

3.4 Monitoring and Treatment Continuation

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.

3.5 Exceptions

If the patient does not meet the criteria for treatment, but the referring clinician believes that there are exceptional grounds for treatment, an Individual Patient Funding Request (IPFR) can be made to WHSSC under the *All Wales Policy for Making Decisions on Individual Patient Funding Requests (IPFR)*.

If the patient wishes to be referred to a provider out of the agreed pathway and the referring clinician believes that there are exceptional grounds for treatment at an alternative provider, an Individual Patient Funding Request (IPFR) can be made to WHSSC under the *All Wales Policy for Making Decisions on Individual Patient Funding Requests (IPFR).*

Guidance on the IPFR process is available at www.whssc.wales.nhs.uk

3.6 Responsibilities

Referrers should:

- Inform the patient that this treatment is not funded outside the criteria in this policy; and
- Refer via the agreed pathway.

Clinicians considering treatment should:

- Discuss all the alternative treatment with the patient;
- Advise the patient of any side effect and risks of the potential treatment;
- Inform the patient that treatment is not routinely funded outside of the criteria in the policy; and
- Confirm that there is contractual agreement with WHSSC for the treatment.

4. QUALITY

Data will be collected from all patients when they start Ataluren treatment and at all subsequent clinic visits.

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.

In line with the Statistical Analysis Plan 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 to 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.

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.

4.1 Clinical Outcome and Quality Measures

- Baseline reports describing the level of mobility must be provided prior to the start of therapy as well as a copy of the signed Managed Access Agreement.
- Patients must attend for regular clinical assessments to confirm compliance and any changes in mobility.
- Annual clinical reports must be provided to WHSSC detailing out-patient attendance, compliance and the level of wheelchair dependence.

- When patients become entirely wheelchair dependant (according to the stopping criteria) confirmation of withdrawal of treatment must be submitted to WHSSC within 1 month of the decision.

4.2 Quality of Life

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.

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.

4.3 Putting Things Right: Raising a Concern

4.3.1 Raising a Concern

Whilst every effort has been made to ensure that decisions made under this policy are robust and appropriate for the patient group, it is acknowledged that there may be occasions when the patient or their representative are not happy with decisions made or the treatment provided. The patient or their representative should be guided by the clinician, or the member of NHS staff with whom the concern is raised, to the appropriate arrangements for management of their concern:

- When a patient or their representative is unhappy with the decision that the patient does not meet the criteria for treatment further information can be provided demonstrating exceptionality. The request will then be considered by the All Wales IPFR Panel.
- If the patient or their representative is not happy with the decision of the All Wales IPFR Panel the patient and/or their representative has a right to ask for this decision to be reviewed. The grounds for the review, which are detailed in the All Wales Policy: Making Decisions on Individual Patient Funding Requests (IPFR), must be clearly stated. The review should be undertaken, by the patient's Local Health Board;
- When a patient or their representative is unhappy with the care provided during the treatment or the clinical decision to withdraw treatment provided under this policy, the patient and/or their representative should be guided to the LHB for NHS Putting Things Right. For services provided outside NHS Wales the patient or their representative should be guided to the NHS Trust Concerns Procedure, with a copy of the concern being sent to WHSSC.

5. EQUALITY IMPACT AND ASSESSMENT

The Equality Impact Assessment (EQIA) process has been developed to help promote fair and equal treatment in the delivery of health services. It aims to enable Welsh Health Specialised Services Committee to identify and eliminate detrimental treatment caused by the adverse impact of health service policies upon groups and individuals for reasons of race, gender re-assignment, disability, sex, sexual orientation, age, religion and belief, marriage and civil partnership, pregnancy and maternity and language (welsh).

This policy has been subjected to an Equality Impact Screening.