GIG CYMRU NHS WALES

Pwyllgor Gwasanaethau Iechyd Arbenigol Cymru (PGIAC)

Welsh Health Specialised Services Committee (WHSSC)

Specialised Services Policy Position Statement PP281

Policy Proposal

Eladocagene exuparvovec for treating aromatic L-amino acid decarboxylase deficiency in people aged 18 months and over

February 2024

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	For action Chief Pharmacists and Clinical Leads Child Health Consultants Consultant Gastroenterologists Consultant Paediatricians Paediatric neurologists Respiratory consultants Endocrinology Consultants Medical Genetics
Description	NHS Wales propose to routinely commission this specialised service in accordance with the criteria described in this policy
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Contents

Policy Statement

Welsh Health Specialised Services Committee (WHSSC) propose to commission eladocagene exuparvovec for treating aromatic L-amino acid decarboxylase deficiency in people aged 18 months and over in accordance with the criteria outlined in this document.

Welsh Language

WHSSC is committed to treating the English and Welsh languages on the basis of equality, and endeavour to ensure commissioned services meet the requirements of the legislative framework for Welsh Language, including the Welsh Language Act (1993), the Welsh Language (Wales) Measure 2011 and the Welsh Language Standards (No.7) Regulations 2018.

Where a service is provided in a private facility or in a hospital outside of Wales, the provisions of the Welsh language standards do not directly apply but in recognition of its importance to the patient experience, the referring health board should ensure that wherever possible patients have access to their preferred language.

In order to facilitate this, WHSSC is committed to working closely with providers to ensure that in the absence of a Welsh speaker, written information will be offered and people have access to either a translator or 'Language-line' if requested. Where possible, links to local teams should be maintained during the period of care.

Decarbonisation

WHSSC is committed to taking assertive action to reducing the carbon footprint through mindful commissioning activities. Where possible and taking into account each individual patient's needs, services are provided closer to home, including via digital and virtual access, with a delivery chain for service provision and associated capital that reflects the WHSSC commitment.

Disclaimer

WHSSC assumes that healthcare professionals will use their clinical judgment, knowledge and expertise when deciding whether it is appropriate to apply this policy position statement.

This policy may not be clinically appropriate for use in all situations and does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian, or Local Authority.

WHSSC disclaims any responsibility for damages arising out of the use or non-use of this policy position statement.

1. Introduction

This Policy Position Statement Proposal has been developed for the planning and delivery of eladocagene exuparvovec for treating aromatic L-amino acid decarboxylase deficiency in people aged 18 months and over resident in Wales. This proposed service will only be commissioned by the Welsh Health Specialised Services Committee (WHSSC) and applies to residents of all seven Health Boards in Wales.

In creating this document WHSSC has reviewed the relevant guidance issued by the National Institute of Health and Care Excellence (NICE)[1] and has concluded that eladocagene exuparvovec for treating aromatic L-amino acid decarboxylase deficiency in people aged 18 months and over should be made available.

1.1 Background

Aromatic L-amino acid decarboxylase deficiency

Aromatic L-amino acid dexarboxylase (AADC) deficiency is an ultra-rare genetic disorder, caused by a mutation of the dopa decarboxylase (DCC) gene. This results in a lack of the AADC enzyme, which leads to severe deficiency in dopamine and other neurotransmitters essential for normal development[1].

This particular deficiency is associated with a wide range of severe symptoms mainly affecting the central nervous system, autonomic nervous system, gastrointestinal system and endocrine system[2]. The condition typically presents from birth, with symptoms becoming apparent in the first few months of life. The condition is often difficult to diagnose because of its rarity and the wide range of possible symptoms. The mean age at diagnosis is usually around 3.5 years, but can range from 2 months to 23 years[1].

AADC deficiency is characterised by oculogyric crises, which are episodes of involuntary muscle spasm, often leading to misdiagnosis of epilepsy, which can delay appropriate treatment. In the UK, a final diagnosis is usually confirmed through genetic testing. The condition commonly leads to decreased muscle tone (hypotonia), movement disorders, developmental delay and restricted growth (failure to thrive). Although there can be a spectrum, approximately 80 percent of people with AADC deficiency present with a phenotype which is clinically severe, broadly defined by international consensus guidelines as reaching no or very limited developmental milestones, and full dependence on carers[1].

[Overview | Eladocagene exuparvovec for treating aromatic L-amino acid decarboxylase deficiency | Guidance | NICE]
[Aromatic L-Amino Acid Decarboxylase Deficiency - Symptoms, Causes, Treatment | NORD (rarediseases.org)]

Premature death (often within the first decade of their lives) is usually from comorbidities such as cardiac events, multiple organ failure, pneumonia, asphyxia and acute complications due to an oculogyric crisis episode. The risk of these comorbidities (and therefore death) decreases as a person moves up through the motor milestones[3].

Current Treatment

There are currently no disease-modifying treatments, no relevant guidelines on AADC deficiency in the UK and no specifically licensed treatments. Current practice is therefore best supportive care. This is highly individualised to the specific symptomatic needs of the child. Management focuses on symptom control using an extensive list of medicines. It involves multidisciplinary team support from specialists, including paediatric neurologists, gastrointestinal specialists, respiratory specialists, endocrinologists, orthopaedic surgeons, speech therapists and physical and occupational therapists[3].

The most commonly used symptomatic treatments all target the dopamine pathway. They include dopamine receptor agonists (to activate postsynaptic dopamine receptors), monoamine oxidase inhibitors (to prevent the breakdown of dopamine and serotonin) and pyridoxine plus pyridoxal phosphate (to increase the activity of the AADC enzyme). None of these symptomatic treatments directly correct the underlying cause of the AADC deficiency[3].

Eladocagene exuparvovec

Eladocagene exuparvov (Upstaza®, PTC Therapeutics Ltd) is the first gene replacement therapy for people with AADC deficiency and the first disease-modifying option[4]. This medicine consists of a modified virus (adeno-associated viral vector) that contains a functional version of the relevant gene. When given to the patient by infusion into the putamen (brain), it will carry the AADC gene into nerve cells enabling them to produce the missing enzyme. This in turn enables the cells to produce the substances they need to function properly (such as dopamine and serotonin), thus improving symptoms of the condition[5]. This medicine has marketing authorisation in the UK for the treatment of patients aged 18 months and older with a clinical, molecular, and genetically confirmed diagnosis of aromatic L-amino acid decarboxylase (AADC) deficiency with a severe phenotype[4].

Overview | Eladocagene exuparvovec for treating aromatic L-amino acid decarboxylase deficiency | Guidance | NICE
Upstaza (Eladocagene exuparvovec) solution for infusion - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk)
Upstaza, INN-eladocagene exuparvovec (europa.eu)

Epidemiology

AADC deficiency is an extremely rare disorder; there are less than 150 patients reported in the literature. AADC deficiency however, is probably underdiagnosed[6]. The estimated prevalence in the U.S. based on cerebrospinal fluid (CSF) analysis and genetic testing is roughly 1-3 in 100,000 live newborns[7]. The predicted birth rate is approximately 1 in 118,000 in the European Union[6].

1.2 Equality Impact 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 subject to an Equality Impact Assessment in line with guidance contained in CPL-026[8].

The Assessment demonstrates the policy is robust and there is no potential for discrimination or adverse impact. All opportunities to promote equality have been taken.

An EQIA was also carried out by NICE during the evaluation of eladocagene exuparvovec. For further details, please refer to the NICE website at: https://www.nice.org.uk/guidance/hst26

Upstaza, INN-eladocagene exuparvovec (europa.eu)
Aromatic L-Amino Acid Decarboxylase Deficiency - Symptoms, Causes, Treatment | NORD (rarediseases.org)
https://whssc.nhs.wales/publications/corporate-policies-and-procedures/corp-26-eqia-policy-v10-final/

2. Recommendations

The recommendations below represent the views of NICE, arrived at after careful consideration of the evidence available. Health professionals are expected to take into account the relevant NICE guidance[9], alongside the individual needs, preferences and values of the patient.

2.1 Inclusion Criteria

Eladocagene exuparvovec is recommended, within its marketing authorisation, as an option for treating aromatic L-amino acid decarboxylase (AADC) deficiency in people 18 months and over with a clinical, molecular and genetically confirmed diagnosis of AADC deficiency with a severe phenotype. Eladocagene exuparvovec is only recommended if the company provides it according to the commercial arrangement[9].

2.2 Monitoring

Healthcare professionals are expected to review a patient's health at regular intervals. Patients undergoing gene therapy should be closely monitored for procedure-related complications, complications related to their underlying disease, and risks associated with general anaesthesia during the peri-operative period[10].

Patients will be offered to enrol in a registry to further evaluate the long-term safety and effectiveness of the treatment under normal conditions of clinical practice[10].

2.3 Acceptance Criteria

The service outlined in this specification is for patients ordinarily resident in Wales, or otherwise the commissioning responsibility of the NHS in Wales. This excludes patients who whilst resident in Wales, are registered with a GP practice in England, but includes patients resident in England who are registered with a GP Practice in Wales.

2.4 Transition arrangements

Transition arrangements should be in line with Transition from children's to adults' services for young people using health or social care services, NICE guidance NG43 and the Welsh Government Transition and Handover Guidance.

Overview | Eladocagene exuparvovec for treating aromatic L-amino acid decarboxylase deficiency | Guidance | NICE
Upstaza (Eladocagene exuparvovec) solution for infusion - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk)

Transition involves a process of preparation for young people and their families for their transition to adulthood and their transition to adult services.

This preparation should start from early adolescence 12-13 year olds. The exact timing of this will ideally be dependent on the wishes of the young person, but will need to comply with local resources and arrangements.

The transition process should be a flexible and collaborative process involving the young person and their family as appropriate and the service.

The way this process is managed will vary on an individual case basis with multidisciplinary input often required and patient and family choice taken into account together with individual health board and environmental circumstances factored in.

2.5 Designated Providers

Great Ormond Street Hospital
Great Ormond Street
London
WC1N 3JH

2.6 Blueteq and reimbursement

Eladocagene exuparvovec will only be funded for patients registered via the Blueteq system and where an appropriately constructed MDT (including paediatric neurology and paediatric metabolic medicine) has approved its use within highly specialised centres.

Where the patient meets the criteria in this policy and the referral is received by an agreed centre, a Blueteq form should be completed for approval. For further information on accessing and completing the Blueteq form please contact WHSSC using the following e-mail address: WHSSC.blueteq@wales.nhs.uk

If a non-contracted provider wishes to treat a patient that meets the criteria they should contact WHSSC (e-mail: WHSSC.IPC@Wales.nhs.uk). They will be asked to demonstrate they have an appropriate MDT in place.

Eladocagene exuparvovec is a single use vial administered by bilateral intraputaminal infusion in one surgical session at two sites per putamen. Four separate infusions of equal volumes are performed. Patients will receive a total dose of 1.8×10^{11} vg delivered as four 0.08mL (0.45×10^{11} vg) infusions (two per putamen).[11]

The posology is the same for the entire population covered by the indication.[11]

The price for a 0.5 ml solution for infusion of eladocagene exuparvovec is £3,010,451 (excluding VAT).[12]

Treatment should be administered in a centre that is specialised in stereotactic neurosurgery, by a qualified neurosurgeon under controlled aseptic conditions.[12]

2.7 Action to be taken

Health Boards and WHSSC are to:

- circulate this Policy Position Statement to all Hospitals/MDTs to inform them of the conditions under which the technology will be commissioned
- ensure that all providers are purchasing eladocagene exuparvovec at the agreed discounted price.

Providers are to:

- ensure the need to approve eladocagene exuparvovec at the appropriate MDT and register use on the Blueteq system. The treatment will only be funded where the Blueteq minimum dataset is fully and accurately populated
- determine estimated patient numbers and the current dose of any patient(s) who will transfer from any company compassionate use scheme or EAMS
- work to written quality standards and provide monitoring information to WHSSC on request.

Upstaza (Eladocagene exuparvovec) solution for infusion - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk)
https://www.nice.org.uk/guidance/hst26

3. Putting Things Right

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.

If 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.

3.2 Individual Patient Funding Request (IPFR)

If the patient does not meet the criteria for treatment as outlined in this policy, an Individual Patient Funding Request (IPFR) can be submitted for consideration in line with the All Wales Policy: Making Decisions on Individual Patient Funding Requests. The All Wales IPFR Panel will then consider the request.

If an IPFR is declined by the Panel, a patient and/or their NHS clinician has the right to request information about how the decision was reached. If the patient and their NHS clinician feel the process has not been followed in accordance with this policy, arrangements can be made for an independent review of the process to be undertaken by the patient's Local Health Board. The ground for the review, which are detailed in the All Wales Policy: Making Decisions on Individual Patient Funding Requests (IPFR), must be clearly stated

If the patient wishes to be referred to a provider outside of the agreed pathway, an IPFR should be submitted.

Further information on making IPFR requests can be found at Welsh Health Specialised Services Committee (WHSSC) | Individual Patient Funding Requests

Annex i Codes

Code Category	Code	Description
ICD	E70.81	Aromatic L-amino acid decarboxylase deficiency