NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technologies Evaluation

Eladocagene exuparvovec for treating aromatic L-amino acid decarboxylase deficiency

Final scope

Remit/evaluation objective

To evaluate the benefits and costs of eladocagene exuparvovec within its marketing authorisation for treating aromatic L-amino acid decarboxylase deficiency for national commissioning by NHS England.

Background

Aromatic L-amino acid decarboxylase (AADC) deficiency is an extremely rare autosomal recessive neurometabolic 'Parkinsonism' disorder. AADC deficiency is caused by mutations in the gene that produces the AADC-enzyme which is involved in the synthesis of the neurotransmitters serotonin and dopamine in the brain. Multiple genetic mutations can cause AADC deficiency, each resulting in different severity of symptoms and levels of response to treatment[1]. Symptoms of AADC deficiency often present in the first year of life and include developmental delays, lack of muscle tone, movement disorders, oculogyric crisis, and problems affecting the autonomic nervous system, such as excessive sweating and nasal congestion[2,3]. Most cases of AADC deficiency present with severe symptoms[3]. It is often difficult to accurately determine prognosis because of variability in the severity of symptoms and the rarity of the condition. Life expectancy for people with AADC deficiency is unknown because of the variability and rarity of the disease but it can result in premature death. While published survival estimates are limited, it is reported that patients with severe AADC deficiency live for less than 10 years from birth[3,5,6]. Most people with AADC deficiency in the UK are children and young adults, but some people with AADC deficiency can live to adulthood.

The disease is reported to have a worldwide incidence of 1 in 55,000,000 with about 150-200 people diagnosed in 30 countries[4]. However, the incidence rate may be higher because there are likely people who are undiagnosed. No UK incidence rate has been reported but there are believed to be less than 10 people with AADC deficiency in the UK. AADC deficiency is more prevalent in people of East Asian family origin[7].

Treatments for AADC deficiency do not treat the underlying cause of the disease and focus on managing symptoms, usually treating dopamine and serotonin deficiency. Medical treatment options include dopamine agonists, monoamine oxidase inhibitors, pyridoxine, anticholinergic agents, folinic acid, L-Dopa, benzodiazepines, and melatonin[3]. Treatment usually involves a combination of drugs depending on symptoms[3]. Other supportive treatments include physiotherapy, speech therapy, occupational therapy, feeding and

nutritional assessment and psychological treatment[3]. Usually, only mild forms of AADC deficiency respond to treatment and not all symptoms can be relieved.

The technology

Eladocagene exuparvovec (Upstaza, PTC Therapeutics) is a single-use gene replacement therapy for people with AADC-deficiency. It is made of a viral vector that has been modified to contain a AADC gene that aims to enable the nerve cells to restore the function of AADC and improve symptoms. The gene therapy is injected via a surgical procedure into an area of the brain called the putamen. Eladocagene exuparvovec uses a viral vector (AAV2), containing the human gene that encodes the AADC enzyme.

Eladocagene exuparvovec does not currently have a marketing authorisation in the UK for the treatment of AADC deficiency. It has been studied in clinical trials in people with AADC deficiency over the age of 2 years old or with a head circumference big enough for surgery.

Intervention(s)	Eladocagene exuparvovec
Population(s)	People with aromatic L-amino acid decarboxylase (AADC) deficiency
Comparators	Established clinical management without eladocagene exuparvovec
Outcomes	The outcome measures to be considered include: • motor function (including, where applicable, age-appropriate motor milestones such as sitting, standing, walking) • autonomic nervous system functioning • speech and language development • cognitive development • body weight • oculogyric crisis • changes in levels of neurotransmitter metabolites in the cerebral spinal fluid • mortality • adverse effects of treatment • health-related quality of life (for patients and carers).
Nature of the condition	• disease morbidity and patient clinical disability with current standard of care

	• impact of the disease on carer's quality of life • extent and nature of current treatment options
Clinical Effectiveness	• overall magnitude of health benefits to patients and, when relevant, carers • heterogeneity of health benefits within the population • robustness of the current evidence and the contribution the guidance might make to strengthen it • treatment continuation rules (if relevant)
Value for Money	• Cost effectiveness using incremental cost per quality-adjusted life year • Patient access schemes and other commercial agreements • The nature and extent of the resources needed to enable the new technology to be used
Impact of the technology beyond direct health benefits	• whether there are significant benefits other than health • whether a substantial proportion of the costs (savings) or benefits are incurred outside of the NHS and personal and social services • the potential for long-term benefits to the NHS of research and innovation • the impact of the technology on the overall delivery of the specialised service • staffing and infrastructure requirements, including training and planning for expertise.
Other considerations	• Guidance will only be issued in accordance with the marketing authorisation. • Guidance will take into account any Managed Access Arrangement for the intervention under evaluation
Related NICE recommendations and NICE Pathways	None.
Related National Policy	NHS England. 2013/14 NHS Standard Contract for Metabolic Disorders (Children). E06/S/b NHS England. 2013/14 NHS Standard Contract for

	Metabolic Disorders (Adult). E06/S/a. NHS England, Manual for prescribed specialised services, 2018/19. Chapters 62 and 134. https://www.england.nhs.uk/wp-content/uploads/2017/10/prescribed-specialised-services-manual.pdf The NHS Long Term Plan, 2019. Section 2.1. NHS Long Term Plan Department of Health and Social Care, NHS Outcomes Framework 2016-2017: Domains 1,2,4,5. https://www.gov.uk/government/publications/nhs-outcomes-framework-2016-to-2017

References

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2 Brun L, Ngu L, Keng W et al. (2010) Clinical and biochemical features of aromatic L-amino acid decarboxylase deficiency. Neurology 75(1): 64-71.

3 Wassenberg T, Molero-Luis M, Jeltsch K et al. (2017) Consensus guideline for the diagnosis and treatment of aromatic L-amino acid decarboxylase (AADC) deficiency. Orphanet Journal of Rare Diseases 12(1): 12.

4 AADC Research Trust website (Accessed 28/04/2021)

5 Hwu W-L, Muramatsu S, Tseng S-H, et al. Gene therapy for aromatic L-amino acid decarboxylase deficiency. Sci Transl Med 2012. 4: 134ra61.

6 Das S, Huang S & Lo AW. Acceleration of rare disease therapeutic development: a case study of AGIL-AADC. Drug Discov Today 2019. 24: 678–684.

7 Hyland K and Reott M (2020) Prevalence of Aromatic L-Amino Acid Decarboxylase Deficiency in At-Risk Populations. Pediatric Neurology 106: 38-42.