NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Eladocagene exuparvovec for treating aromatic L-amino acid decarboxylase deficiency

Draft scope

Draft remit/evaluation objective

To appraise the clinical and cost effectiveness of eladocagene exuparvovec within its marketing authorisation for treating aromatic L-amino acid decarboxylase deficiency.

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, 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.

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. AADC deficiency is more prevalent in people of East Asian family origin[5].

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 with or without carbidopa, 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 with clinical characteristics of severe AADC deficiency.

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 • mortality • adverse effects of treatment • health-related quality of life (for patients and carers).

Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.
Other considerations	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.
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

Questions for consultation

What is the approximate number of people with AADC deficiency in the UK?

Are the clinical trial results generalisable to the population who would be treated in the UK?

How would you define a mild, moderate or severe disease phenotype?

What proportion of people with AADC deficiency in the UK have a severe disease phenotype?

What is the life expectancy for people with a mild, moderate or severe disease phenotype?

Would eladocagene exuparvovec be used to treat people with AADC deficiency with a mild or moderate disease phenotype?

Did the clinical trials include people who would be considered to have mild to severe AADC deficiency disease phenotype?

Have all relevant comparators for eladocagene exuparvovec been included in the scope?

Which treatments are considered to be established clinical practice in the NHS for AADC deficiency?

Are the outcomes listed appropriate?

Are there any subgroups of people in whom eladocagene exuparvovec is expected to provide greater clinical benefits or more value for money, or other groups that should be examined separately?

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which eladocagene exuparvovec will be licensed;

- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;

- could have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

Do you consider eladocagene exuparvovec to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a ‘step-change’ in the management of the condition)?

Do you consider that the use of eladocagene exuparvovec can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?

Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.

To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly.

NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on the Institute's Technology Appraisal processes is available at http://www.nice.org.uk/article/pmg19/chapter/1-Introduction).

References

1 Helman G, Pappa M, and Pearl P (2014) Widening Phenotypic Spectrum of AADC Deficiency, a Disorder of Dopamine and Serotonin Synthesis. JIMD Reports 17: 23-27.

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