Anthem

Medical Policy

Subject: Gene Therapy for Aromatic L-Amino Acid Decarboxylase Deficiency
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Description/Scope

This document addresses gene therapy for aromatic l-amino acid decarboxylase (AADC) deficiency, which is a genetic disease involving variations in the human dopa decarboxylase (DDC) gene that reduce an individual's ability to synthesize dopamine and serotonin from their precursor molecules. These chemicals are essential neurotransmitters that control many vital physiological functions such as sleep, memory, learning, brain development and cardiovascular function. A gene therapy product to treat AADC deficiency has been approved by the U.S. Food and Drug Administration (FDA), eladocagene exuparvovec-tneq (Kebilidi™). In Kebilidi therapy, an adeno-associated virus vector containing a functional copy of the human DDC gene is delivered directly into the brain through stereotactic injections. The viral vector infects the brain's cells and causes a switch in the target genetic code, with the goal of allowing nerve cells to produce the missing enzyme.

Position Statement

Investigational and Not Medically Necessary:

Gene therapy for aromatic l-amino acid decarboxylase deficiency using eladocagene exuparvovec-tneq is considered **investigational and not medically necessary** for all indications.

Rationale

Viral vector gene therapy

Gene therapy for AADC deficiency involves a non-replicating recombinant adeno-associated virus serotype 2 (AAV2) based vector containing the DNA of the human DDC gene under the control of the cytomegalovirus immediate-early promoter. The modified AAV2 virus is delivered as gene therapy directly into the brain through stereotactic injections. The one-time treatment is designed to correct the underlying genetic defect by delivering a functioning DDC gene directly into the putamen, a structure in the brain that plays a role in motor control, learning, speech, and other important physiological functions. The concept is that the AADC enzyme is then properly expressed in the brain cells, dopamine production is restored, and the symptoms of AADC deficiency are ameliorated.

Eladocagene exuparvovec-tneq

Eladocagene exuparvovec-tneq (Kebilidi) is a gene therapy medicinal product comprised of a genetically engineered AAV2 vector that expresses the human AADC enzyme (AAV2-hAADC). It is produced in vitro in human embryonic kidney cells by recombinant DNA technology. The product contains 2.8×10^{11} vector genomes (vg)/0.5 mL solution for infusion. It is administered by a qualified neurosurgeon via stereotactic injection into the brain as a bilateral infusion (2 infusions per putamen). A total dose of 1.8×10^{11} vg is delivered as four 0.08 mL (0.45×10^{11} vg) infusions (two per putamen).

In a published report detailing the use of eladocagene exuparvovec-tneq gene therapy to treat human AADC deficiency, 26 individuals without head control received bilateral intraputaminal infusions of the product and completed 1-year follow-up evaluations (Tai, 2022). These individuals were enrolled in one of three consecutive trials that employed the same treatment protocol (compassionate use [n=8], phase I/II [NCT01395641; n=10], and phase IIb [NCT02926066; n=8]). A confirmed diagnosis of severe AADC deficiency was needed for inclusion by fulfilling all of the following requirements:

- Decreased levels of homovanillic acid (HVA) and 5-hydroxyindoleacetic acid (5-HIAA) in cerebrospinal fluid (CSF)
- Increased levels of blood or CSF 3-O-methyldopa (3-OMD)

- Presence of at least one pathogenic DDC gene variant
- Classical symptoms of AADC deficiency

All individuals were at least 2 years old or, if younger, had skull bones suitable for the surgery (closed anterior fontanelle). The oldest participants were aged 8 years. All enrolled individuals were of Chinese descent except for one who identified as Caucasian/Thai.

Results showed that dopamine production was increased after eladocagene exuparvovec-tneq treatment. Analysis of CSF HVA and 5-HIAA reflect the levels of dopamine and serotonin in the brain, respectively. Before gene therapy, individuals had very low levels of HVA in the CSF (mean ± SD, 6.6 ± 11.2 nmol/L), but the levels increased to 30.2 ± 16.7 nmol/L one year after gene therapy ($p<0.001$). CSF levels of 5-HIAA did not significantly increase after gene therapy. Evidence of *de novo* dopamine production was derived from positron emission tomography (PET) imaging with a ^{18}F-DOPA tracer that can be converted to ^{18}F-dopamine by AADC activity and taken up by nerve cells in the putamen. At baseline, individuals had a mean ^{18}F-DOPA-specific uptake of 0.23 ± 0.14 (n=24) that increased at 12 months (0.48 ± 0.24; n=24, $p<0.001$), 2 years (0.55 ± 0.24; n=15; $p=0.003$), and 5 years (0.60 ± 0.20; n=13; $p<0.001$) after gene therapy. PET data at 5 years were said to demonstrate the durability of the gene therapy effects and were consistent with motor function milestone development.

The Peabody Developmental Motor Scales–Second Edition (PDMS-2) and the Alberta Infant Motor Scale (AIMS) tools were used to measure children's motor ability. Before gene therapy, individuals had a very low mean baseline PDMS-2 score of 10.4 ± 5.4 (n=25). Healthy 3-year-old children may have a score of 400. The baseline PDMS-2 score increased rapidly at 1 year (80.5 ± 43.4; n=25), 2 years (114.5 ± 55.2; n=22), and 5 years after gene therapy (116.1 ± 59.8; n =11) ($p< 0.01$ for all comparisons vs. baseline). Cognitive and language functions were assessed using the Bayley Scale of Infant and Toddler Development, Third Edition (Bayley-III). The Bayley-III cognitive score increased from baseline (11.2 ± 3.0; n=18) at 1 year (23.2 ± 6.4; n=18; $p<0.001$), 2 years (27.3 ± 7.4; n=16; $p<0.001$), and 5 years (27.8 ± 9.7; n=6; $p=0.006$). The Bayley-III language scores similarly increased after gene therapy from baseline (17.2 ± 2.8; n=18) to 1 year (24.6 ± 2.6; n=18; $p< 0.001$), 2 years (26.9 ± 5.0; n=16; $p< 0.001$), and 5 years (27.9 ± 3.6; n=6; $p= 0.007$). Healthy 3-year-old children may have a score of 70.

The safety of eladocagene exuparvovec-tneq treatment was also evaluated. The procedure to administer eladocagene exuparvovec-tneq involves invasive stereotactic neurosurgery to inject the genetically modified viral particles into the brain through an intracranial cannula. Potential risks of this procedure include CSF leakage, intracranial hemorrhage, infection, anemia, and wound complications. Ten individuals experienced adverse events related to the surgery, including 3 with CSF leakage, but all resolved. All participants experienced at least one treatment-emergent adverse event (TEAE) during the study. The two most commonly reported TEAEs were fever and dyskinesia. Most dyskinesia events were mild or moderate in severity and occurred within 3 months of eladocagene exuparvovec-tneq administration. Most participants had a positive anti-AAV2 antibody response within the first year after treatment, but immune responses to the viral vector are not expected to affect localized brain gene therapy. Two participants who achieved walking backwards at week 48 were treated before 2 years of age. The four participants who were unable to achieve new gross motor milestones at week 48 were treated between the ages of 2.8 and 10.8 years.

However, despite the promising results in terms of efficacy and safety in these early trials of eladocagene exuparvovec-tneq, the extent to which this approach is capable of changing the natural history of AADC deficiency in most affected individuals is unclear and will strongly depend on the ability to identify and treat this disorder shortly after its initial presentation and before the onset of brain damage (Himmelreich, 2019). Although symptoms of AADC deficiency emerge within the first year of life, nearly all individuals with this condition experience significant delays in accurate diagnosis. Tai and colleagues (2022) found that younger age was associated with greater improvement after eladocagene exuparvovec-tneq treatment. The increase in PDMS-2 total scores had a negative correlation with age, indicating that younger individuals exhibited faster and greater improvements after eladocagene exuparvovec-tneq gene therapy. Currently, individuals aged less than 1.5 years are not able receive this therapy due to surgical technical limitations owing to the unstable skull structure of the partially fused anterior fontanel.

Furthermore, there is limited clinical evidence for benefit of dopamine agonists and monoamine oxidase (MAO) inhibitors, which target the same biological pathways as eladocagene exuparvovec-tneq therapy. All of these treatments seek to elevate neurotransmitter activity in the brain. Dopamine agonists activate dopamine receptors and MAO inhibitors prevent the breakdown of serotonin and dopamine. However, the evidence for effectiveness of medical therapies has been limited, with respect to both the proportion of responders and the degree of observed symptomatic improvement. These drug therapies have been evaluated only in small case series or uncontrolled studies, and the quality of the resulting evidence

is regarded as low or very low, in addition to providing little guidance as to optimal dosage or duration/frequency of treatment (Himmelreich, 2019).

The durability of treatment with eladocagene exuparvovec-tneq is also in question. Participants in the compassionate use study (n=5) have been followed the longest, for a period of 6-10 years. Participants had variable results at long-term follow-up, with 3 individuals having stable functional PDMS-2 and AIMS scores and 2 others showing a decline in motor function 3-5 years after gene therapy (Tai, 2022).

On July 18, 2022, eladocagene exuparvovec (marketed in Europe with the brand name Upstaza™) received its first approval by the European Medicines Agency. It was approved for use in individuals aged 18 months and older with a clinical, molecular, and genetically confirmed diagnosis of AADC deficiency with a severe phenotype (that is, who cannot sit, stand or walk). There is limited experience in people aged 12 years and older, and the safety and efficacy of Upstaza in these individuals have not been established. The product was approved for one-time administration only; repeat administration of Upstaza and its use for the treatment of other indications has not been evaluated.

On November 13, 2024, the FDA approved a single-dose intraputaminal infusion of Kebilidi for the following indication: “KEBILIDI (eladocagene exuparvovec-tneq) is an adeno-associated virus (AAV) vector-based gene therapy indicated for the treatment of adult and pediatric patients with aromatic L-amino acid decarboxylase (AADC) deficiency.” Kebilidi is contraindicated for individuals who have not achieved skull maturity assessed by neuroimaging.

The following warnings and precautions for Kebilidi were listed in the product insert:

- Procedural complications: Monitor patients for procedural complications for neurosurgery, including events of respiratory and cardiac arrest after administration of KEBILIDI. (5.1)
- Dyskinesia: Monitor patients for dyskinesia after treatment with KEBILIDI. The use of dopamine antagonists can be used to control dyskinesia symptoms. (5.2)

In the product insert, the FDA cited one open-label, single arm study that evaluated the efficacy of Kebilidi (NCT04903288). The study enrolled 13 pediatric individuals aged 1.3 to 10.8 years with genetically confirmed, severe AADC deficiency who had achieved skull maturity assessed with neuroimaging. The main outcome measure was gross motor milestone achievement evaluated at week 48 and assessed using the PDMS-2. One participant dropped out of the study before week 48. Eight (67%) of the 12 treated individuals who were assessed at week 48 achieved a new gross motor milestone. Two participants who achieved walking backwards at week 48 were treated before 2 years of age. The four participants who were unable to achieve new gross motor milestones at week 48 were treated between the ages of 2.8 and 10.8 years. There was no comparison group which limits the generalizability of the study.

In summary, while eladocagene exuparvovec-tneq therapy appears to impact some symptoms of AADC deficiency, it does not address all aspects of the enzyme deficiency since the treatment is limited to one brain structure. There is a wide range of clinical presentations of this condition and diagnosis is often difficult and delayed, possibly hindering optimal timing of delivery of gene therapy. There is limited evidence for clinical benefit of AADC treatments that target dopaminergic pathways. This gene therapy can only be administered at highly specialized treatment centers by a neurosurgeon experienced in stereotactic neurosurgeries and capable of delivering infusions to the putamen. Administration of this gene therapy to the putamen does not increase levels of serotonin, which is produced in the brainstem. Long term outcomes of this therapy are uncertain.

Background/Overview

Aromatic L-amino acid decarboxylase (AADC) deficiency is a rare, fatal, inborn error of neurotransmitter biosynthesis affecting the central nervous system (CNS). Mutations in the dopa decarboxylase (DDC) gene alter or abolish the activity of the AADC enzyme leading to a reduction in CNS levels of neurotransmitters such as dopamine, noradrenalin (norepinephrine), adrenalin (epinephrine), serotonin, and melatonin (Keam, 2022). A total of 82 DDC gene variants leading to AADC deficiency have been identified for all known individuals with this condition (n=123) (Himmelreich, 2019).

Most individuals with AADC deficiency show severe disability from the first months of life, fail to achieve developmental milestones, and frequently cannot sit, stand or walk. Signs and symptoms of AADC deficiency include loss of head control or other early motor skills, speech loss, involuntary eye movements where eyes suddenly roll upwards, excessive crying, sweating and drooling, sleep disturbances, feeding difficulties, intellectual disability, frequent vomiting, and behavioral problems. There is wide variability in the clinical presentation of AADC deficiency, and the intensity of individual symptoms in specific cases can range from mild to very severe. Individuals with AADC deficiency are at a high risk of early death in the first decade of life (Simons, 2023).

A definitive diagnosis of AADC deficiency is made by fulfilling all of the following criteria: decreased levels of CSF homovanillic acid (HVA; a dopamine metabolite) and 5-hydroxyindoleacetic acid (5-HIAA; a serotonin metabolite), elevated blood or CSF levels of 3-O-methyldopa (3-OMD), the presence of at least one pathogenic variant in the DDC gene, and classical symptoms of AADC deficiency (Wassenberg, 2017).

There is no curative treatment for AADC deficiency. Treatment of symptoms using combinations of vitamin B6, dopamine agonists and monoamine oxidase inhibitors (all recommended as first-line treatments) has shown only limited success, especially in cases where individuals have severe impairments (Himmelreich, 2019). Ongoing physical, occupational, and speech therapy and other interventions are required to manage severe complications such as infections, feeding difficulties and breathing problems which may be life-threatening (Keam, 2022).

AADC deficiency is an ultra-rare condition estimated to affect fewer than 50 people in the United States (DiBacco, 2023). The actual prevalence may be higher, around 1-2 per million in the U.S., as it is likely underdiagnosed or misdiagnosed due to similarity with other conditions (NORD, 2024). AADC deficiency is more prevalent in Asian populations (especially Taiwanese and Japanese), probably due to a founder effect (Wassenberg, 2017). In Taiwan, the incidence of cases from 1996 to 2022 was 1:88,538 births (Hwu, 2023).

AADC deficiency is inherited in an autosomal recessive manner. An individual will be affected if a disease-causing gene variant is inherited from each parent. Individuals with one altered copy of the gene and one normal copy are carriers for the disease, but are generally asymptomatic (NORD, 2024).

Definitions

Autosomal recessive disorder: An inherited condition for which two copies of an abnormal gene must be present in order for the disease or trait to develop.

Dyskinesia: A movement disorder that causes involuntary muscle movements, such as tics, tremors, or shakes.

Gene therapy: A medical treatment that introduces or alters genetic material to replace the function of a missing or dysfunctional gene with the goal of lessening or eliminating a disease process that results from genetic dysfunction.

Neurotransmitter: A chemical substance that is made and released by nerve cells causing the transfer of nerve impulses to another nerve fiber, a muscle fiber, or some other structure.

Putamen: A round structure in the brain that plays a role in motor control, learning, speech articulation and other physiological functions controlled by the neurotransmitter dopamine. There is one putamen on each side of the brain, for a total of two.

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

When services are Investigational and Not Medically Necessary:
For the following procedure codes; or when the code describes a procedure indicated in the Position Statement section as investigational and not medically necessary.

CPT	
64999	Unlisted procedure; nervous system [when specified as administration of a gene therapy]
HCPCS	
	For the following HCPCS codes when specified as eladocagene exuparvovec:
C9399	Unclassified drugs or biologicals
J3490	Unclassified drugs
J3590	Unclassified biologics
ICD-10 Procedure	

XW0Q316	Introduction of eladocagene exuparvovec into cranial cavity and brain, percutaneous approach, new technology group 6

ICD-10 Diagnosis

All diagnoses

References

Peer Reviewed Publications:

1. DiBacco ML, Hinahara J, Goss TF, Pearl PL. Burden of illness in aromatic l-amino acid decarboxylase deficiency. Ann Child Neurol Soc. 2023; 1(1):75–78.
2. Himmelreich N, Montioli R, Bertoldi M, et al. Aromatic amino acid decarboxylase deficiency: molecular and metabolic basis and therapeutic outlook. Mol Genet Metab. 2019; 127(1):12–22.
3. Hwu W-L, Hsu R-H, Li M-H, et al. Aromatic l-amino acid decarboxylase deficiency in Taiwan. JIMD Rep. 2023; 64(5):387–392.
4. Keam SJ. Eladocagene exuparvovec: First approval. Drugs. 2022; 82:1427–1432.
5. Simons CL, Hwu W-L, Zhang R, et al. Long-term outcomes of eladocagene exuparvovec compared with standard of care in aromatic l-amino acid decarboxylase (AADC) deficiency: A modelling study. Adv Ther. 2023; 40:5399–5414.
6. Tai C-H, Lee N-C, Chien Y-H, et al. Long-term efficacy and safety of eladocagene exuparvovec in patients with AADC deficiency. Mol Ther. 2022; 30(2):509–518.
7. Wassenberg T, Molero-Luis M, Jeltsch K, et al. Consensus guideline for the diagnosis and treatment of aromatic l-amino acid decarboxylase (AADC) deficiency. Orphanet J Rare Dis. 2017; 12:12.

Government Agency, Medical Society, and Other Authoritative Publications:

1. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Available at: https://clinicaltrials.gov/ct2/home. Accessed on September 5, 2024.
    - A Phase I/II Clinical Trial for Treatment of Aromatic L-amino Acid Decarboxylase (AADC) Deficiency Using AAV2-hAADC. NCT01395641.
    - A Clinical Trial for Treatment of Aromatic L-amino Acid Decarboxylase (AADC) Deficiency Using AAV2-hAADC - An Expansion. NCT02926066.
    - A Study of SmartFlow Magnetic Resonance (MR) Compatible Ventricular Cannula for Administering Eladocagene Exuparvovec to Pediatric Participants. NCT04903288.
2. European Medicines Agency. Upstaza product information. Last updated: March 26, 2024. Available at: https://www.ema.europa.eu/en/documents/product-information/upstaza-epar-product-information_en.pdf. Accessed on September 4, 2024.
3. U.S. Food and Drug Administration. KEBILIDI™ highlights of prescribing information. Revised 11/2024. Available at: https://www.fda.gov/media/183530/download?attachment. Accessed on November 19, 2024.

Websites for Additional Information

1. National Library of Medicine. Aromatic l-amino acid decarboxylase deficiency. Last updated: May 13, 2024. Available at: https://medlineplus.gov/genetics/condition/aromatic-l-amino-acid-decarboxylase-deficiency/. Accessed on September 5, 2024.
2. National Organization for Rare Disorders (NORD). Aromatic l-amino acid decarboxylase deficiency. Last updated: July 30, 2024. Available at: https://rarediseases.org/rare-diseases/aromatic-l-amino-acid-decarboxylase-deficiency/. Accessed on September 3, 2024.

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The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

Document History

Status	Date	Action
New	11/22/2024	Medical Policy & Technology Assessment Committee (MPTAC) review. Initial document development.
Preliminary Discussion	11/14/2024	MPTAC pre-FDA approval review.
