BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

EVIDENCE-BASED CRITERIA	**ORIGINAL EFFECTIVE DATE: 02/20/25**
SECTION: SPECIALTY MEDICAL DRUGS	**LAST REVIEW DATE:**
	CURRENT EFFECTIVE DATE: 02/20/25
	LAST CRITERIA REVISION DATE:
NEXT ANNUAL REVIEW DATE: 1st QTR 2026	**ARCHIVE DATE:**

GENE THERAPY FOR AROMATIC L AMINO ACID DECARBOXYLASE (AADC)

- **KEBILIDI™ (eladocagene exuparvovec-tneq)**

Non-Discrimination Statement is located at the end of this document.

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Evidence-Based Criteria must be read in its entirety to determine coverage eligibility, if any.

This Evidence-Based Criteria provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.

The section identified as "Description" defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as "Criteria" defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Evidence-Based Criteria are subject to change as new information becomes available.

For purposes of this Evidence-Based Criteria, the terms "experimental" and "investigational" are considered to be interchangeable.

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Criteria:

Refer to FDA website for current indications and dosage.

- **Criteria for initial therapy:** Kebilidi (eladocagene exuparvovec-tneq) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

  1. Prescriber is a physician specializing in aromatic L amino acid decarboxylase (AADC) deficiency or is in consultation with a Pediatric Neurologist or Neurosurgeon

  2. Individual is between 16 months and 17 years of age or older

  3. Individual has a confirmed diagnosis of severe aromatic L amino acid decarboxylase (AADC) deficiency with **ALL** of the following:

     - Genetic testing confirms compound heterozygous or homozygous pathogenic variants in the *dopa decarboxylase (DDC)* gene
     - Decreased AADC enzyme activity in plasma
     - Clinical characteristics of AADC deficiency (e.g., hypertonia, hypotonia, delayed motor development, autonomic symptoms including ptosis, excessive sweating, temperature instability, etc.)
     - Persistent neurological defects secondary to AADC deficiency despite standard medical therapy (dopamine agonists, monoamine oxidase inhibitor, pyridoxine, or other forms of vitamin B6)
     - Unable to ambulate independently (with or without assistive device)
     - Achieved skull maturity assessed by neuroimaging

  4. Individual does **NOT** have **ANY** of the following:

     - Clinically active infection
     - Prior gene therapy or is being considered for treatment with any other gene therapy
     - Pyridoxine 5'-phosphate oxidase or tetrahydrobiopterin (BH4) deficiency
     - Anti-adeno-associated virus, serotype 2 (anti-AAV2) antibody titer higher than 1:1200 or >1 optical density value by enzyme-linked immunosorbent assay

  5. There are **NO** contraindications including individuals who have not achieved skull maturity assessed by neuroimaging

  Approval duration: **ONE** injection per lifetime.
  The safety and effectiveness of repeat administrations of Kebilidi (eladocagene exuparvovec-tneq) have not been evaluated.

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- Kebilidi (eladocagene exuparvovec-tneq) for all other indications not previously listed is considered ***experimental or investigational*** and will not be covered when any **ONE** or more of the following criteria are met:

  1. Lack of final approval from the appropriate governmental regulatory bodies (e.g., Food and Drug Administration); or
  2. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes; or
  3. Insufficient evidence to support improvement of the net health outcome; or
  4. Insufficient evidence to support improvement of the net health outcome as much as, or more than, established alternatives; or
  5. Insufficient evidence to support improvement outside the investigational setting.

  These indications include, *but are not limited to:*

  - Treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, or duration
  - Use of Kebilidi in individuals with mild or moderate disease
  - Use in individuals 18 years of age or older

Description:

Aromatic L-amino acid decarboxylase deficiency (AADCD) is a rare, autosomal, recessive disorder that results from biallelic mutations in the *DDC* gene, leading to a deficiency in the aromatic L-amino acid decarboxylase (AADC) enzyme. A deficiency in the AADC enzyme results in deficiencies in dopamine, epinephrine, norepinephrine, and serotonin. Clinical manifestations of AADCD include developmental delay (including delay or lack of motor milestone achievement), hypotonia, autonomic dysfunction, sleep abnormalities and irritability. AADCD is classified into three main phenotypes, mild, moderate and severe. The severe phenotype describes children who are unable to achieve any motor milestones (with gross motor function limited to poor or no head control), have severe hypotonia, feeding difficulties, oculogyric crises (dystonic movements of the eye, face, neck that can last for several hours and occur several times per week), and autonomic dysfunction. Individuals with the severe phenotype are completely dependent on caregivers for activities of daily living and experience early mortality in childhood due to these impairments. The mild phenotype includes individuals who have less gross motor impairment and can achieve the ability to ambulate independently. Some of these individuals with mild disease, who can live into adulthood, may not have any motor impairments and experience primarily autonomic dysfunction as well as sleep and behavioral disturbances. The moderate phenotype describes individuals who achieve some motor milestones (i.e., head control, sitting, standing) but are unable to master independent ambulation. Prior to gene therapy, there were no FDA-approved therapies for AADCD. Dopamine agonists, monoamine oxidase inhibitors (MAOIs), and pyridoxine (B6) are used off-label and are considered the current standard of care therapies. Individuals with mild and moderate disease generally have a positive response in motor function with these therapies.

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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. This indication is approved under accelerated approval based on the change from baseline in gross motor milestone achievement at 48 weeks post treatment. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory clinical trial.

Kebilidi is administered via four infusions in one surgical session into a large structure in the brain involved in motor control. Kebilidi should be administered in a medical center that specializes in pediatric stereotactic neurosurgery - a technique that uses imaging and special equipment to deliver therapies to specific areas in the brain. After infusion of Kebilidi, treatment results in the expression of AADC and subsequent increase in the production of dopamine, a critical neurotransmitter in the brain associated with movement, attention, learning and memory.

Kebilidi is currently being studied in an ongoing trial in 13 pediatric individuals with severe AADCD. The primary efficacy outcome was decrease in homovanillic acid (HVA) in the CSF which is a main metabolite of dopamine and was considered as a proxy for dopamine levels in the brain. However, during the Food and Drug Administration (FDA) review of the gene therapy, this surrogate marker was determined to be an insufficient endpoint to reasonably predict clinical benefit. The FDA determined that the secondary endpoint of major motor milestone achievement compared to historical controls did establish a benefit and therefore granted accelerated approval with verification needed in confirmatory trial. The FDA granted approval in pediatric and adults though the pivotal open-label trial was only done in non-ambulatory pediatric patients with severe disease.

Definitions:

First line drugs to treat AADC deficiency (Off-Label)

Class	Drug
Vitamin B6	Pyridoxine
	Pyridoxal 5-phosphate
Dopamine agonists	Pramipexole
	Ropinirole
	Rotigotine patch
	Bromocriptine
MAO-inhibitors	Selegiline
	Tranylcypromine

History:	Date:	Activity:
Pharmacy and Therapeutics Committee	02/20/25	Approved guideline
Clinical Pharmacist	01/16/25	Development

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Coding:

HCPCS: C9399, J3590

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Literature reviewed 02/20/25. We do not include marketing materials, poster boards and non-published literature in our review.

1. Kebilidi (eladocagene exuparvovec-tneq). Prescribing information, PTC Therapeutics, Inc. November 2024, at DailyMed http://dailymed.nlm.nih.gov. Accessed January 16, 2025.

2. 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(1):12.

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Blue Cross Blue Shield of Arizona (BCBSAZ) complies with applicable Federal civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability or sex. BCBSAZ provides appropriate free aids and services, such as qualified interpreters and written information in other formats, to people with disabilities to communicate effectively with us. BCBSAZ also provides free language services to people whose primary language is not English, such as qualified interpreters and information written in other languages. If you need these services, call (602) 864-4884 for Spanish and (877) 475-4799 for all other languages and other aids and services.

If you believe that BCBSAZ has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability or sex, you can file a grievance with: BCBSAZ's Civil Rights Coordinator, Attn: Civil Rights Coordinator, Blue Cross Blue Shield of Arizona, P.O. Box 13466, Phoenix, AZ 85002-3466, (602) 864-2288, TTY/TDD (602) 864-4823, crc@azblue.com. You can file a grievance in person or by mail or email. If you need help filing a grievance BCBSAZ's Civil Rights Coordinator is available to help you. You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights electronically through the Office for Civil Rights Complaint Portal, available at https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at: U.S. Department of Health and Human Services, 200 Independence Avenue SW., Room 509F, HHH Building, Washington, DC 20201, 1–800–368–1019, 800–537–7697 (TDD). Complaint forms are available at http://www.hhs.gov/ocr/office/file/index.html