Utilization Review Policy 358

POLICY: Neurology – Gene Therapy – Kebilidi Utilization Management Medical Policy
- Kebilidi® (eladocagene exuparvovec-tneq suspension for intraputaminal infusion – PTC Therapeutics)

EFFECTIVE DATE: 5/1/2025
LAST REVISION DATE: 01/29/2025

COVERAGE CRITERIA FOR: All UCare Plans

OVERVIEW

Kebilidi, an adeno-associated virus vector-based gene therapy, is indicated for the treatment of aromatic L-amino acid decarboxylase (AADC) deficiency in adult and pediatric patients.[1] The indication is approved under accelerated approval based on change from baseline in gross motor milestone achievement at 48 weeks after administration of Kebilidi. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory clinical trial.

Kebilidi is given as a single-dose intraputaminal infusion only.[1] The total recommended dose is 1.8×10^{11} vector genomes (0.32 mL) which is administered by four intraputaminal infusions in a single stereotactic neurosurgical procedure. Kebilidi is intended to be given with an infusion pump that is able to permit infusion at a rate of 0.003 mL/minute. Two infusions are delivered in the anterior putamen and two in the posterior putamen. At each target point, the duration of the infusion is 27 minutes. Kebilidi should be administered only using an FDA-authorized cannula for intraparenchymal infusion. This gene therapy should be given in a medical center that specializes in stereotactic neurosurgery. It should be confirmed that the patient has AADC deficiency due to biallelic mutations in the dopa decarboxylase (*DDC*) gene. Of note, the safety and effectiveness of Kebilidi have not been studied in pediatric patients < 16 months of age.

Disease Overview

Aromatic L-amino acid decarboxylase deficiency is a rare genetic neurological disorder that is caused by pathogenic variants in the *DDC* gene that encodes for the AADC enzyme.[2-5] AADC enzyme deficiency leads to an inability to synthesize dopamine and serotonin from their precursors. The onset of the condition is usually in early infancy. Impacted patients may experience various complex symptoms such as delays in gross motor function (head control, standing, and walking), hypotonia (weak muscle tone), and developmental and/or cognitive delays. Complications may be life-threatening.[2-5] In the US, the estimated newborn at-risk population for AADC deficiency is around 1/42,000 to 1/90,000 births.[6] The Peabody Developmental Motor Scale, Second Edition (PDMS-2) is a tool utilized to evaluate patient response.[7] The overall PDMS-2 involves six subtests that evaluate motor abilities that develop early in life (e.g., grasping, visual-motor integration, reflexes, stationary, locomotion, and object manipulation).

Clinical Efficacy

Kebilidi was assessed for efficacy in one open-label, single-arm study that involved 13 pediatric patients (median age of 2.8 years [range 1.3 to 10.8 years]).[1] Patients had achieved skull maturity assessed by neuroimaging. Genetic confirmation of AADC deficiency was required[1] and patients also had decreased AADC enzyme activity in plasma.[8] Patients also must have had persistent neurologic defects secondary to AADC deficiency despite standard medical therapy (e.g., dopamine agonists, monoamine oxidase [MAO] inhibitors, pyridoxine).[8] Gross motor milestone achievement was assessed at Week 48 utilizing the PDMS-2.[1] Comparisons with patients given Kebilidi were made to an external untreated natural history cohort involving 43 pediatric patients who had severe AADC deficiency. At Week 48, assessment of gross motor

milestone achievement occurred in 12 of the 13 patients treated with Kebilidi. In total, 67% of the treated patients achieved a new gross motor milestone at Week 48 (e.g., head control, sitting [with or without assistance], ability to walk backwards). In comparison with the 43 untreated patients with the severe phenotype, none of the patients experienced motor milestone achievement at last assessment at a median age of 7.2 years (range 2 to 19 years).[1] Other data are also available that describe the effects of Kebilidi in patients with AADC deficiency.[2]

Guidelines

Current guidelines do not address Kebilidi. A consensus guideline for the diagnosis and treatment of AADC deficiency is available from the International Working Group on Neurotransmitter Related Disorders (2017).[5] Many recommendations are provided. In most patients, AADC deficiency can be confirmed by genetic testing. The three main diagnostic elements for this condition include the following: 1) decreased AADC enzyme activity in plasma; 2) compound heterozygous or homozygous pathogenic variants in the *DDC* gene; and 3) examination of cerebral spinal fluid (CSF) neurotransmitter levels. Of note, CSF neurotransmitter levels that suggest a diagnosis of AADC deficiency are low levels of 5-hydroxyindoleacetic acid, homovanillic acid, and 3-methoxy 4-hydroxyphenylglycol; increased levels of 3-O-methyldopa, 3,4-dihydroxyphenylalanine, and 5-hydroxytryptophan; and normal CSF pterins. It is recommended that genetic testing be performed and at least two of the three diagnostic tests cited above be positive. First-line treatments for AADC deficiency are dopamine agonists, MAO inhibitors (e.g., tranylcypromine, selegiline), and pyridoxine. Among the dopamine agonists, non-ergot derived agents are preferred (e.g., pramipexole, ropinirole, rotigotine). Cabergoline and pergolide should not be utilized due to the high risk of fibrotic complications. Although there is limited evidence regarding clinical benefit, MAO inhibitors should be tried in patients as these agents prevent the breakdown of dopamine and serotonin. Vitamin B6 is considered a first-line treatment from a biochemical standpoint. However, dose limits should be considered due to adverse events. In addition, anticholinergic medications can be considered for management of various symptoms (e.g., autonomic symptoms).

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Kebilidi. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Because of the specialized skills required for evaluation and diagnosis of patients treated with Kebilidi as well as the specialized training required for administration of Kebilidi, approval requires Kebilidi to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for one-time (per lifetime) as a single dose. If claims history is available, verification is required for certain criteria, as noted by **[verification in claims history required]**. For dosing criteria, verification is required by the Medical Director as noted by **[verification required]**.

All reviews (approvals and denials) will be forwarded to the Medical Director for evaluation. Some clients have elected Embarc Benefit Protection. For these clients, the Medical Director will coordinate with eviCore to ensure the Embarc Benefit Protection portion of the review has been completed. If the Embarc Benefit Protection portion of the review has not been completed, the Medical Director will route to Embarc@eviCore.com prior to completing the review.

Documentation: Documentation is required for use of Kebilidi as noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, laboratory tests, medical test results, claims records, prescription receipts, and/or other information.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Kebilidi is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Aromatic L-Amino Acid Decarboxylase Deficiency.** Approve a one-time (per lifetime) single dose if the patient meets ALL of the following (A, B, C, D, E, F, G, and H):
   - **A)** Patient is ≥ 16 months of age; AND
   - **B)** Patient has achieved skull maturity as evaluated by neuroimaging **[documentation required]**; AND
   - **C)** Patient has not received Kebilidi in the past **[verification in claims history required]**; AND
     Note: If no claim for Kebilidi is present (or if claims history is not available), the prescribing physician confirms that the patient has not previously received Kebilidi.
   - **D)** Patient has biallelic pathogenic variants in the dopa decarboxylase (*DDC)* gene **[documentation required]**; AND
   - **E)** Patient has decreased aromatic L-amino acid decarboxylase (AADC) enzyme activity in plasma per current laboratory standards **[documentation required]**; AND
   - **F)** According to the prescribing physician, the patient has continued symptoms of AADC deficiency despite use of at least one standard medication therapy; AND
     Note: Examples of medications used for AADC deficiency include dopamine agonists (e.g., pramipexole, ropinirole, rotigotine), monoamine oxidase inhibitors (e.g., tranylcypromine, selegiline), pyridoxine, and other forms of vitamin B6.
   - **G)** The medication is prescribed by a neurologist or a neurosurgeon; AND
   - **H)** If criteria A through G are met, approve one dose of Kebilidi to provide for a one-time (per lifetime) single dose. The total recommended dose is 1.8×10^{11} vector genomes (0.32 mL) which is administered by four intraputaminal infusions (0.08 mL each at a dose of 0.45×10^{11} vector genomes) in a single stereotactic neurosurgical procedure **[verification required]**.

   Dosing. The recommended dose of Kebilidi is a one-time (per lifetime) single dose which provides a total of 1.8×10^{11} vector genomes (0.32 mL) which is administered by four intraputaminal infusions (0.08 mL each at a dose of 0.45×10^{11} vector genomes) in a single stereotactic neurosurgical procedure.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Kebilidi is not recommended in the following situations:

1. **Prior Receipt of Gene Therapy.** This was an exclusion criterion in the pivotal study.

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Kebilidi™ suspension for intraputaminal infusion [prescribing information]. Warren, NJ: PTC Therapeutics; November 2024.
2. Tai CH, Lee NC, Chien YH, et al. Long-term efficacy and safety of eladocagene exuparvovec in patients with AADC deficiency. *Mol Ther.* 2022;30(2):509-518.
3. Blau N, Pearson TS, Kurian MA, Elsea SH. Aromatic L-Amino Acid Decarboxylase Deficiency. 2023 Oct 12 [updated 2025 Jan 23]. In: Adam MP, Feldman J, Mirzaa GM, Pagon RA, Wallace SE, Amemiya A, editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2025.

4. Lee HM, Mercimek-Andrews S, Horvath G, et al. A position statement on the post gene-therapy rehabilitation of aromatic l-amino acid decarboxylase deficiency in patients. *Orphanet J Rare Dis.* 2024;19:17.
5. 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.
6. Himmelreich N, Bertoldi M, Alfadhel M, et al. Prevalence of DDC genotypes in patients with aromatic L-amino acid decarboxylase (AADC) deficiency and *in silico* prediction of structural protein changes. *Mol Genet Metab.* 2023;139(3):107624.
7. Folio MR, Fewell RR. Peabody Developmental Motor Scales-2 second edition. Examiner's manual. Austin, TX: Pro-ED;2000.
8. PTC Therapeutics. A study of smartflow magnetic resonance compatible ventricular cannula for administering eladocagene exuparvovec to pediatric participants. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000- [cited 2025 Jan 1]. Available at: https://www.clinicaltrials.gov/study/NCT04903288?term=eladocagene%20exuparvovec&rank=1. NLM Identifier: NCT04903288.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	01/29/2025
UCare P&T Review	Policy reviewed and approved by UCare P&T committee. Annual review process	03/10/2025