Blue Cross Blue Shield Blue Care Network of Michigan

Nonprofit corporations and independent licensees of the Blue Cross and Blue Shield Association

Medical benefit drug policies are a source for BCBSM and BCN medical policy information only. These documents are not to be used to determine benefits or reimbursement. Please reference the appropriate certificate or contract for benefit information. This policy may be updated and therefore subject to change.

Effective Date: 12/12/2024

Kebilidi™ (eladocagene exuparvovec-tneq)

HCPCS: J3590

Policy:

Requests must be supported by submission of chart notes and patient specific documentation.

A. Coverage of the requested drug is provided when all the following are met:
   a. FDA approved indication
   b. FDA approved age
   c. Prescribed by or in consultation with a pediatric neurologist
   d. Diagnosis must be confirmed based on all of the following:
      i. Genetic testing showing biallelic mutations in the DOPA decarboxylase (DDC) gene
      ii. Reduced levels of 5-hydroxyindoleacetic acid (5-HIAA), homovanillic acid (HVA) and 3-methoxy-4-hydroxyphenylglycol (MHPG) and high concentrations of 3-O-methyldopa (3-OMD), L-Dopa, and 5-OH tryptophan (5-HTP) in the cerebral spinal fluid (CSF)
      iii. Reduced aromatic L-amino acid decarboxylase (AADC) activity in the plasma
   e. Must present with classical clinical characteristics of AADC deficiency, such as oculogyric crises, hypotonia, and developmental delay
   f. Must not have any significant structural brain abnormality
   g. Must not have an anti-AAV2 neutralizing antibody titer over 1,200 folds
   h. Have not received prior treatment with any other AAV2-based gene therapy despite indication or are being considered for treatment with any other AAV2-based gene therapy
   i. The requesting physician attests to providing clinical outcome information within the appropriate provider portal as requested by BCBSM
   j. Trial and failure, intolerance, or a contraindication to the preferred products as specified in the BCBSM/BCN medical utilization management drug list

B. Quantity Limitations, Authorization Period and Renewal Criteria
   a. Quantity Limits: Align with FDA recommended dosing
   b. Authorization Period: 3 months with the allowance of only one dose per lifetime
   c. Renewal Criteria: Not applicable as no further authorization will be provided

***Note: Coverage and approval duration may differ for Medicare Part B members based on any applicable criteria outlined in Local Coverage Determinations (LCD) or National Coverage Determinations (NCD) as determined by Center for Medicare and Medicaid Services (CMS). See the CMS website at http://www.cms.hhs.gov/. Determination of coverage of Part B drugs is based on medically accepted indications which have supported citations included or approved for inclusion determined by CMS approved compendia.

Background Information:

- Aromatic L-amino acid decarboxylase (AADC) deficiency is an autosomal recessive ultrarare disorder caused by a mutation on the DOPA decarboxylase (DDC) gene. It is characterized by a dysfunctional AADC enzyme which is responsible for the production of the neurotransmitters dopamine, serotonin, epinephrine, and norepinephrine. When the enzyme is not functional or has decreased activity, a smaller number of these neurotransmitters are produced leading to neurons not being able to communicate and send signals properly throughout the body.

- The symptoms of AADC deficiency typically begin shortly after birth or when the child is a few months old. There is a wide range of possible symptoms, and the severity of the disease varies among affected individuals. The two most common symptoms are hypotonia in the trunk and oculogyric crises. These crises are characterized by abnormal rotation of the eyeballs and gaze deviation, uncontrolled movements of the head and neck, muscle spasms, agitation, and irritability. They can last several hours and tend to recur every 2 to 5 days. Other movement disorders can be present, such as, hypokinesia, hypertonia in the limbs, dystonia, athetosis, chorea, and tremors. Dysfunction of the autonomic nervous system can lead to excessive sweating, hypersalivation, ptosis, nasal congestion, temperature instability, hypotension, and hypoglycemia. Gastrointestinal symptoms including gastric reflux, constipation, or diarrhea are common. Because of the disease itself and because of the numerous possible symptoms, children with AADC deficiency have developmental delays and are not able to reach normal milestones such as walking and talking, have feeding difficulties, and experience a failure to thrive. They are prone to many medical complications and might also have difficulty adapting to those complications as their autonomic nervous system is dysfunctional and can react inappropriately to stressors such as surgery or infections.

- The 2017 consensus guidelines for the diagnosis and treatment of AADC deficiency state confirmation of disease involves three core diagnostic tests: a lumbar puncture showing cerebral spinal fluid (CSF) with low levels of 5-hydroxyindoleacetic acid (5-HIAA), homovanillic acid (HVA) and 3-methoxy-4-hydroxyphenylglycol (MHPG) and high concentrations of 3-O-methyldopa (3-OMD), L-Dopa, and 5-OH tryptophan (5-HTP); genetic testing showing mutations in the DCC gene; and decreased AADC enzyme activity in the plasma. If genetic diagnosis is performed as the first step, functional confirmation should be completed by measuring AADC enzyme activity in the plasma and/or neurotransmitter metabolites in CSF. Guidelines do recommend performing all three diagnostic tests to confirm diagnosis.

- Until now, there have been no disease modifying therapies available for the treatment of AADC deficiency. Management has included a multidisciplinary approach to address the specific needs of the affected individual. Numerous medications can help manage symptoms although the most appropriate treatment regimen greatly varies among affected individuals. There is limited scientific evidence for the efficacy of most treatment options due to the rarity of the disease. First-line treatments include dopamine agonists, monoamine oxidase B [MAO-B] inhibitors, and vitamin B6. Guidelines prefer the use of non-ergot derived dopamine agonists including pramipexole, ropinirole, and rotigotine, and state they should be tried. Guidelines also recommend a trial of MAO-B inhibitors although literature support for use is minimal. Vitamin B6 is considered due to its use as a cofactor for the AADC enzyme and the possibility it may increase residual enzyme activity. Other medications may also be considered for treatment of patient specific symptoms, such as, melatonin, benzodiazepines, or anticholinergics.

- Kebilidi is the first disease modifying therapy approved for the treatment of adult and pediatric patients with AADC deficiency. It is an adeno-associated virus (AAV) vector-based gene therapy that replaces the disfunction DDC gene in AADC patients with a functional copy.

- Safety and efficacy of Kebilidi was evaluated in in an open-label, single arm, natural history cohort study of 13 pediatric patients with genetically confirmed, severe AADC deficiency who had achieved skull maturity assessed with neuroimaging. Twelve of the 13 patients had the severe phenotype of AADC deficiency, defined as having no motor milestone achievement at baseline and no clinical response to standard of care therapies. The one remaining patient had a "variant" of the severe disease phenotype with the ability to sit with assistance but with lack of head control. Patients were excluded from the trial if they had any significant structural brain abnormality or had an anti-AAV2 neutralizing antibody titer over 1,200 folds. Patients received a single total dose of 1.8×10^{11} vg of Kebilidi given as four intraputaminal infusions in a single stereotactic neurosurgical procedure. Patients treated with Kebilidi were compared to an external untreated natural history cohort of 43 pediatric patients with severe AADC deficiency who had at least one motor milestone assessment after 2 years of age. The primary endpoint was gross motor milestone achievement evaluated at week 48 and assessed using the Peabody Developmental Motor Scale, Second Edition (PDMS-2). Gross motor milestone achievement at Week 48 was assessed in 12 of the 13 patients treated in the study with one patient dropping out prior to week 48. Eight (67%) of the 12 treated patients achieved a new gross motor milestone at week 48: 3 patients achieved full head control, 2 patients achieved sitting with or without assistance, 2 patients achieved walking backwards, and the patient with the "variant" severe phenotype was able to sit unassisted. The two patients who achieved walking backwards at week 48 were treated before 2 years of age. The four patients who were unable to achieve new gross motor milestones at week 48 were treated between the ages of 2.8 and 10.8 years. In comparison, none of the 43 untreated patients with the severe phenotype had documented motor milestone achievement at last assessment at a median age of 7.2 years (range 2 to 19 years)

- Kebilidi uses an AAVs vector to deliver a functional copy of the DDC gene to the patient's brain where functional AADC enzyme is produced. Patients with high AAV2 antibody titers may not respond to gene therapy due to the antibodies neutralizing Kebilidi before the functional DDC gene can be properly incorporated into the patient's genome. The Kebilidi study excluded patients from the trial based on antibody titers greater than 1200 fold.

- Kebilidi has not been studied and there is no data to support use in combination with other gene therapies indicated for use in AADC deficiency.

- Provider portal platforms allow the capture of clinical outcome information for patients on select high-cost treatments, such as gene and cellular therapies. If a patient meets medical necessity as defined by this policy and is approved for treatment, the requesting physician must attest to providing clinical outcome information within the appropriate provider portal at the requested cadence.

References:

1. Kebilidi [prescribing information]. Warren, NJ: PTC Therapeutics, Inc.; November 2024.
2. Clinicaltrials.gov. An open-label trial to address the safety of the SmartFlow MR-compatible ventricular cannula for administering eladocagene exuparvovec to pediatric subjects (NCT04903288). Available at: https://clinicaltrials.gov/study/NCT04903288. Accessed on November 14, 2024.
3. Chien YH, Lee NC, Tseng SH, et al. AGIL-AADC gene therapy results in sustained improvements in motor and developmental milestones over 5 years in children with AADC deficiency. Neuro. 2019 April 9; 92 (Suppl 15): 4.6 – 058.
4. Hwu PWL, Chein YH, Lee NC, et al. Safety and improved efficacy outcomes in children AADC deficiency treated with eladocagene exuparvovec gene therapy: results from three clinical trials. Neuro. 2020 April 14; 94 (Suppl 15): 4688.
5. Chien YH, Lee NC, Tseng SH, et al. Efficacy and safety of AAV2 gene therapy in children with aromatic L-amino acid decarboxylase deficiency: an open-label, phase 1/2 trial. Lancet Child Adolesc Health. 2017 Dec 1; 1 (4): 265-273.
6. Leveille E & Blau N. Aromatic l-amino acid decarboxylase deficiency. 2024 Nov 14. Available at: https://rarediseases.org/rare-diseases/aromatic-l-amino-acid-decarboxylase-deficiency/. Accessed on November 14, 2024.

7. Hyland K & Reott M. Prevalence of aromatic l-amino acid decarboxylase deficiency in at-risk populations. Ped Neuro. 2020 May; 106: 38 – 42.
8. 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 Dec; 12 (1): 12 – 33.
9. Tai CH, Lee NC, Chien YH, et al. Long-term efficacy and safety of eladocagene exuparvovec in patients with AADC deficiency. Molecular Ther. 2022 Feb; 30 (2): 509- 18.

<table>
<tr><th colspan="3">Policy History</th></tr>
<tr><th>#</th><th>Date</th><th>Change Description</th></tr>
<tr><td>1.7</td><td>Effective Date: 02/03/2025</td><td>UM medical management system update for MAPPO and BCNA
<table><tr><th>Line of Business</th><th>PA Required in Medical Management System (Yes/No)</th></tr><tr><td>BCBS</td><td>Yes</td></tr><tr><td>BCN</td><td>Yes</td></tr><tr><td>MAPPO</td><td>Yes</td></tr><tr><td>BCNA</td><td>Yes</td></tr></table></td></tr>
<tr><td>1.6</td><td>Effective Date: 12/12/2024</td><td>New policy - this criteria replaces previously approved preliminary criteria.</td></tr>
<tr><td>1.5</td><td>Effective Date: 11/22/2024</td><td>UM medical management system update for BCBS and BCN
<table><tr><th>Line of Business</th><th>PA Required in Medical Management System (Yes/No)</th></tr><tr><td>BCBS</td><td>Yes</td></tr><tr><td>BCN</td><td>Yes</td></tr><tr><td>MAPPO</td><td>No</td></tr><tr><td>BCNA</td><td>No</td></tr></table></td></tr>
<tr><td>1.4</td><td>Effective Date: 04/11/2024</td><td>Annual review of criteria was performed, no changes were made</td></tr>
<tr><td>1.3</td><td>Effective Date: 04/06/2023</td><td>Updated approval duration to 3 months</td></tr>
<tr><td>1.2</td><td>Effective Date: 08/04/2022</td><td>Annual review - No changes to the criteria at this time</td></tr>
<tr><td>1.1</td><td>Effective Date: 08/12/2021</td><td>Annual review - No changes to the criteria at this time</td></tr>
<tr><td>1.0</td><td>Effective Date: 08/13/2020</td><td>Preliminary drug review
<table><tr><th>Line of Business</th><th>PA Required in Medical Management System (Yes/No)</th></tr><tr><td>BCBS</td><td>No</td></tr><tr><td>BCN</td><td>No</td></tr><tr><td>MAPPO</td><td>No</td></tr><tr><td>BCNA</td><td>No</td></tr></table></td></tr>
</table>

** The prescribing information for a drug is subject to change. To ensure you are reading the most current information it is advised that you reference the most updated prescribing information by visiting the drug or manufacturer website or http://dailymed.nlm.nih.gov/dailymed/index.cfm.*