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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.

P&T Date: 12/04/2025

Kebilidi™ (eladocagene exuparvovec-tneq)

HPCPS: 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:
- Coverage of the requested drug is considered investigational/experimental for all indications due to insufficient evidence of a clinical benefit
 - BCBSM and BCN are awaiting the results of ongoing clinical trials to provide evidence of a clinical benefit

***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

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AADC deficiency have developmental delays and are not able to reach normal milestones such as walking and talking, have feeding difficulties, and experience 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 DDC 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.
- Management includes 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 a 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 dysfunction DDC gene in AADC patients with a functional copy. This indication is approved under accelerated approval based on 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.
- Safety and efficacy of Kebilidi was evaluated 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 intraputamenal 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 surrogate 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).

- The plan considers cellular and gene therapies to be proven effective to treat a condition if the following are true: the drug has full Food and Drug Administration approval that was not obtained under the FDA's accelerated approval pathway and the drug met all of its primary endpoint(s) in its pivotal trials, or if confirmatory trials were required, the drug met its primary endpoint(s) in its confirmatory trial(s). Cellular and gene therapies that haven't been proven effective (do not meet the listed criteria) are considered a benefit contract exclusion for most plans.
- Kebilidi was approved under the FDA's accelerated approval pathway, and therefore, is considered experimental/investigational until further confirmatory trials are complete and the medication gets full FDA approval.

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 eladocogene exuparvec 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 eladocogene exuparvec 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 eladocogene exuparvec in patients with AADC deficiency. *Molecular Ther*. 2022 Feb; 30 (2): 509- 18.

Policy History												
#	Date	Change Description										
1.8	Effective Date: 01/20/2026 P&T Date: 12/04/2025	Updated to experimental/investigational designation										
1.7	Effective Date: 02/03/2025	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>	Line of Business	PA Required in Medical Management System (Yes/No)	BCBS	Yes	BCN	Yes	MAPPO	Yes	BCNA	Yes
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BCBS	Yes											
BCN	Yes											
MAPPO	Yes											
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1.6	Effective Date: 12/12/2024	New policy - this criteria replaces previously approved preliminary criteria.										
1.5	Effective Date: 11/22/2024	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>	Line of Business	PA Required in Medical Management System (Yes/No)	BCBS	Yes	BCN	Yes	MAPPO	No	BCNA	No
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MAPPO	No											
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1.4	Effective Date: 04/11/2024	Annual review of criteria was performed, no changes were made										
1.3	Effective Date: 04/06/2023	Updated approval duration to 3 months										
1.2	Effective Date: 08/04/2022	Annual review - No changes to the criteria at this time										
1.1	Effective Date: 08/12/2021	Annual review - No changes to the criteria at this time										
1.0	Effective Date: 08/13/2020	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>	Line of Business	PA Required in Medical Management System (Yes/No)	BCBS	No	BCN	No	MAPPO	No	BCNA	No
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MAPPO	No											
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* 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>.

Blue Cross Blue Shield/Blue Care Network of Michigan

Medication Authorization Request Form



This form is to be used by participating physicians to obtain coverage for **drugs covered under the medical benefit**. For commercial members only, please complete this form and submit via fax to 1-877-325-5979. If you have any questions regarding this process, please contact BCBSM Provider Relations and Servicing or the Medical Drug Helpdesk at 1-800-437-3803 for assistance.

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PATIENT INFORMATION	PHYSICIAN INFORMATION
Name	Name
ID Number	Specialty
D.O.B. ☐ Male ☐ Female	Address
Diagnosis	City /State/Zip
Drug Name	Phone/Fax: P: () - F: () -
Dose and Quantity	NPI
Directions	Contact Person
Date of Service(s)	Contact Person Phone / Ext.

STEP 1: DISEASE STATE INFORMATION

- Is this request for: ☐ Initiation ☐ Continuation Date patient started therapy: _____
- Administered by patient or a medical professional? ☐ patient (self) ☐ health care professional (physician, nurse, etc.)
- Site of administration? ☐ Provider office/Home infusion ☐ Other: _____
☐ Hospital outpatient facility (go to #4) Reason for Hospital Outpatient administration: _____
☐ Hospital inpatient facility for Car-T therapy only (for example: Kymriah, Yescarta, or Tecartus) (go to #5)
- Please specify location of administration if hospital outpatient infusion: _____
- Please specify location of administration if hospital inpatient infusion: _____
- Please provide the NPI number for the place of administration: _____
- Initiation AND Continuation of therapy:**
 - What is the patient's diagnosis? _____
 - What other medication has the patient received for their condition? Please list _____
 - Please describe the response to previous therapies: _____
 - Will the patient be receiving any other treatment for the listed condition while on this medication? Please list: _____
 - Please list any labs values important for diagnosing or monitoring this patient's condition: _____
- Continuation of therapy:**
 - Has the patient progressed while on this medication? ☐ yes ☐ no
 - How has the patient's condition changed while on this medication?

☐ Improved: Please describe: _____
 ☐ Stable: please describe: _____
 ☐ Worsened; Please describe: _____
 ☐ Other; Please describe: _____

Chart notes are required for the processing of all requests. Please add any other supporting medical information necessary for our review (required)

Coverage will not be provided if the prescribing physician's signature and date are not reflected on this document.

☐ Request for expedited review: I certify that applying the standard review time frame may seriously jeopardize the life or health of the member or the member's ability to regain maximum function

Physician's Name	Physician Signature	Date
Step 2: Checklist	☐ Form Completely Filled Out ☐ Provide chart notes	☐ Attach test results
Step 3: Submit	By Fax: BCBSM Specialty Pharmacy Mailbox 1-877-325-5979	By Mail: BCBSM Specialty Pharmacy Program P.O. Box 312320, Detroit, MI 48231-2320

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7/26/2018, 9/18/2018; 1/31/2020; 3/17/2020; 8/9/2021