Daybue (trofinetide) Prior Authorization with Quantity Limit Program Summary

This program applies to MN Medicaid.

POLICY REVIEW CYCLE

Effective Date	Date of Origin
04-01-2024	10-01-2023

FDA APPROVED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Daybue™ (trofinetide) Oral solution	Treatment of Rett syndrome in adults and pediatric patients 2 years of age and older		1

See package insert for FDA prescribing information: https://dailymed.nlm.nih.gov/dailymed/index.cfm

CLINICAL RATIONALE

Rett Syndrome	Rett syndrome (RTT) is a rare X-linked neurodevelopmental disorder characterized by loss of speech and purposeful hand use, with the development of distinctive hand movements and gait abnormalities. Until methyl-CpG-binding protein 2 (MECP2) was identified as the causative gene, diagnosis had been based only on consensus clinical criteria which had key clinical elements that identify classic/typical RTT, but also variant/atypical forms. Because the MECP2 mutation is the most commonly observed cause of RTT, the disease caused by the MECP2 mutation is called classic/typical RTT. Mutation screening identifies MECP2 gene alterations in 95–97% of patients with classical/typical RTT, though MLPA testing may be needed to detect deletions otherwise missed by genetic sequencing.(2,7,8) Whereas MECP2 mutation is the classic/typical RTT, the similar clinical manifestations involving other genes is historically called the atypical RTT (e.g., CDKL5 mutation, FOXG1 mutation). Mutations in CDKL5 and FOXG1 have resulted in unique diseases that are distinguishable from RTT, since the specific symptoms of the disease vary depending on the causative gene involved. For example, mutations in CDKL5 cause early life epilepsy, while those in FOXG1 are known to cause characteristic stereotypic movements and severe microcephaly. The diseases caused by CDKL5 and FOXG1 mutations are referred to as CDD (CDKL5 deficiency disorder) and FOXG1 syndrome, respectively. Because an effective treatment for these diseases is yet to be found, elucidation of the molecular signaling pathways controlled by the driver genes is an important prerequisite for the development of viable therapies.(3,4,5) Symptoms of RTT include loss of purposeful hand skills, loss of spoken language, gait abnormalities, abnormal hand movements, breathing distubances, impaired sleep, growth retardation, abnormal muscle tone, and seizures.(7,8)
Efficacy	The mechanism by which trofinetide exerts therapeutics effects in patients with Rett syndrome is unknown.(1) Trofinetide is a novel synthetic analog of glycine-proline-glutamate (GPE), the N-terminal tripeptide of insulin-like growth factor 1 (IGF-1).(6) There is evidence that the level of IGF-1 is decreased in the cerebrospinal fluid of RTT patients. Supplementing with IGF-1 can improve motor function, respiration, anxiety, and other behaviors, as well as prolong the life span of RTT mice. In clinical trials, recombinant human IGF-1 can improve abnormal respiratory movement, cognitive ability, irritability, and anxiety in RTT patients.(10)

	The efficacy of Daybue for the treatment of Rett syndrome was established in a 12-week randomized, double-blind, placebo-controlled study in patients with Rett syndrome 5 to 20 years of age (Study 1; NCT04181723). Patients (N=187) had a diagnosis of typical Rett syndrome according to the Rett Syndrome Diagnostic Criteria with a documented disease-causing mutation in the MECP2 gene. Patients were randomized to receive Daybue (N=93) or matching placebo (N=94) for 12 weeks. The Daybue dosage was based on patient weight to achieve similar exposure in all patients.(1) The co-primary efficacy measures were change from baseline after 12 weeks of treatment in the total score of the Rett Syndrome Behaviour Questionnaire (RSBQ) and the Clinical Global Impression-Improvement (CGI-I) score. The RSBQ is a 45-item rating scale completed by the caregiver that assesses a range of symptoms of Rett syndrome (breathing, hand movements or stereotypies, repetitive behaviors, night-time behaviors, vocalizations, facial expressions, eye gaze, and mood). The Clinical Global Impression scale (CGI) is a clinician-rated scale used to rate patients' global functioning before and after treatment in trials, assessing whether a patient has improved or worsened.(1,9) Treatment with Daybue demonstrated a statistically significant difference in favor of Daybue as compared to placebo on the co-primary efficacy endpoints, the change from baseline in RSBQ total score and the CGI-I score at week 12.(1)
Safety	Daybue has no FDA labeled contraindications.(1)

REFERENCES

Number	Reference
1	Daybue prescribing information. Acadia Pharmaceuticals Inc. March 2023.
2	Guerrini R, Parrini E. Epilepsy in Rett Syndrome, and CDKL5- and FOXG1-Gene-Related Encephalopathies. Epilepsia. 2012 Sep;53(12):2067-2078.
3	Percy AK, Neul JL, Peters S, et al. Current Status of Developmental Encephalopathies: Rett Syndrome, MECP2 Duplication Disorder, CDKL5 Deficiency Disorder, and FOXG1 Disorder. Transl Sci Rare Dis. 2023 Jan;1-28.
4	Akol I, Gather F, Vogel T. Paving Therapeutic Avenues for FOXG1 Syndrome: Untangling Genotypes and Phenotypes from a Molecular Perspective. Int J Mol Sci. 2022 Jan;23(2):954.
5	Ma M, Adams HR, Seltzer LE, et al. Phenotype Differentiation of FOXG1 and MEPC2 Disorders: A New Method for Characterization of Developmental Encephalopathies. J Pediatr. 2016 Nov;178:233-240.
6	Neul JL, Percy AK, Benke TA, et al. Design and Outcome Measures of LAVENDER, A Phase 3 Study of Trofinetide for Rett Syndrome. Contemp Clin Trials. 2022 Mar;114.
7	International Rett Syndrome Foundation. Rett Syndrome: Primary Care Guidelines. Available at: https://www.rettsyndrome.org/wp-content/uploads/IRSF_PrimaryCareGdlns_REV2021.pdf
8	Fu C, Armstrong D, Marsh E, et al. Consensus Guidelines on Managing Rett Syndrome Across the Lifespan. BMJ Paediatr Open. 2020 Sep;4(1).
9	Singh J, Fiori F, Law ML, et al. Development and Psychometric Properties of the Multi-System Profile of Symptoms Scale in Patients with Rett Syndrome. J Clin Med. 2022;11:1-19.
10	Yuan ZF, Mao SS, Shen J, et al. Insulin-Like Growth Factor-1 Down-Regulates the Phosphorylation of FXYD1 and Rescues Behavioral Deficits in a Mouse Model of Rett Syndrome. Neurosci. 2020 Jan;14.

POLICY AGENT SUMMARY PRIOR AUTHORIZATION

Target Brand Agent(s)	Target Generic Agent(s)	Strength	Targeted MSC	Available MSC	Final Age Limit	Preferred Status

Target Brand Agent(s)	Target Generic Agent(s)	Strength	Targeted MSC	Available MSC	Final Age Limit	Preferred Status
Daybue	trofinetide oral soln	200 MG/ML	M ; N ; O ; Y	N		

POLICY AGENT SUMMARY QUANTITY LIMIT

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	QL Amount	Dose Form	Day Supply	Duration	Addtl QL Info	Allowed Exceptions	Targeted NDCs When Exclusions Exist
Daybue	trofinetide oral soln	200 MG/ML	8	Bottles	30	DAYS			

CLIENT SUMMARY – PRIOR AUTHORIZATION

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Client Formulary
Daybue	trofinetide oral soln	200 MG/ML	Medicaid

CLIENT SUMMARY – QUANTITY LIMITS

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Client Formulary
Daybue	trofinetide oral soln	200 MG/ML	Medicaid

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval

Initial Evaluation

Target Agent(s) will be approved when ALL of the following are met:

1. ONE of the following:
   A. The requested agent is eligible for continuation of therapy AND ONE of the following:

Agents Eligible for Continuation of Therapy
Daybue

      1. Information has been provided that indicates the patient has been treated with the requested agent (starting on samples is not approvable) within the past 90 days **OR**
      2. The prescriber states the patient has been treated with the requested agent (starting on samples is not approvable) within the past 90 days AND is at risk if therapy is changed **OR**

   B. BOTH of the following:
      1. The patient has a diagnosis of classic/typical Rett syndrome (RTT) **AND**
      2. The patient has a disease-causing mutation in the MECP2 gene **AND**
2. If the patient has an FDA approved indication, then ONE of the following**:**
   A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR**
   B. The prescriber has provided information in support of using the requested agent for the patient's age for the requested indication **AND**

Module	Clinical Criteria for Approval
	3. The patient's weight is 9 kg or greater **AND** 4. The prescriber has assessed baseline status (prior to therapy with the requested agent) of the patient's RTT symptoms (e.g., speech patterns, hand movements, gait, growth, muscle tone, seizures, breathing patterns, quality of sleep **AND** 5. The prescriber is a specialist in the area of the patient's diagnosis (e.g., geneticist, neurologist, pediatrician) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 6. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 3 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria. **Renewal Evaluation** **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process **AND** 2. The patient has had clinical benefit with the requested agent (e.g., speech patterns, hand movements, gait, growth, muscle tone, seizures, breathing patterns, quality of sleep) **AND** 3. The prescriber is a specialist in the area of the patient's diagnosis (e.g., geneticist, neurologist, pediatrician) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 4. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Quantity limit for the Target Agent(s) will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. ALL of the following: A. The requested quantity (dose) exceeds the program quantity limit **AND** B. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** C. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **OR** 3. ALL of the following: A. The requested quantity (dose) exceeds the program quantity limit **AND** B. The requested quantity (dose) exceeds the maximum FDA labeled dose for the requested indication **AND** C. The prescriber has provided information in support of therapy with a higher dose for the requested indication **Length of Approval:** Initial: 3 months; Renewal: 12 months