Drug Coverage Policy

Effective Date.....06/15/2026
Coverage Policy Number IP0578
Policy Title .....Daybue

Neurology – Daybue

- Daybue® (trofinetide oral solution – Acadia)
- Daybue® Stix (trofinetide powder for oral solution – Acadia)

INSTRUCTIONS FOR USE
The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Each coverage request should be reviewed on its own merits. Medical directors are expected to exercise clinical judgment where appropriate and have discretion in making individual coverage determinations. Where coverage for care or services does not depend on specific circumstances, reimbursement will only be provided if a requested service(s) is submitted in accordance with the relevant criteria outlined in the applicable Coverage Policy, including covered diagnosis and/or procedure code(s). Reimbursement is not allowed for services when billed for conditions or diagnoses that are not covered under this Coverage Policy (see "Coding Information" below). When billing, providers must use the most appropriate codes as of the effective date of the submission. Claims submitted for services that are not accompanied by covered code(s) under the applicable Coverage Policy will be denied as not covered. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Overview
Daybue is indicated for the treatment of Rett syndrome in adults and pediatric patients ≥ 2 years of age.[1]

Disease Overview
Rett syndrome is a neurodevelopmental disorder characterized by typical early growth and development followed by a slowing of development, loss of functional use of the hands, distinctive hand movements, slowed brain and head growth, problems with walking, seizures, and intellectual disability.[2] The course of Rett syndrome, including the age of onset and the severity of symptoms, varies from child to child. However, symptoms of Rett syndrome usually appear in children between 6 to 18 months as they begin to miss developmental milestones or lose abilities they had gained.[3] Rett syndrome occurs worldwide in 1 of every 10,000 to 15,000 female births and is even rarer in males. Rett syndrome is estimated to affect all racial and ethnic groups worldwide.[2] Nearly all cases of Rett syndrome are caused by a variant in the methyl CpG binding protein 2 (*MECP2*) gene. The *MECP2* gene contains instructions for the synthesis of a protein called methyl cytosine binding protein 2 (MeCP2), which is needed for brain development and acts as a biochemical switch that can increase or decrease gene expression.

Typical, or classic, Rett syndrome is defined by the presence of the characteristic disease progression of Rett syndrome, a period of regression followed by recovery or stabilization.[4,5] The diagnosis of classic/typical Rett syndrome requires all main diagnostic criteria and none of the exclusion criteria. The main Rett syndrome diagnostic criteria are: 1) partial or complete loss of acquired purposeful hand skills; 2) partial or complete loss of acquired spoken language; 3) gait abnormalities, i.e., impaired (dyspraxic) or absence of ability; and 4) stereotypic hand movements, such as hand wringing/squeezing, clapping/tapping, mouthing and washing/rubbing automatisms. The exclusion criteria for classic/typical Rett syndrome are: 1) brain injury secondary to trauma (peri- or postnatally), neurometabolic disease, or severe infection that causes neurological problems; and 2) grossly abnormal psychomotor development in first 6 months of life. Additionally, clinicians have also identified individuals that display some, but not all, of the features of typical Rett syndrome.[4] These individuals are described to have atypical, or variant, Rett syndrome. Atypical Rett syndrome is defined by the presence of a period of regression followed by recovery or stabilization, as well as at least 2 of the main 4 criteria for typical Rett syndrome and at least 5 of the 11 supporting criteria: breathing disturbances when awake; bruxism when awake; impaired sleep pattern; abnormal muscle tone; peripheral vasomotor disturbances; scoliosis/kyphosis; growth retardation; small cold hands and feet; inappropriate laughing/screaming spells; diminished response to pain; and intense eye communication, use of eye pointing.[5]

Because *MECP2* variants are now identified in some individuals prior to any clear evidence of regression, the diagnosis of "possible" Rett syndrome should be given to those individuals < 3 years of age who have not lost any skills but otherwise have clinical features suggestive of Rett syndrome.[5] These individuals should be reassessed every 6 to 12 months for evidence of regression. If regression manifests, the diagnosis should then be changed to definite Rett syndrome. However, if the child does not show any evidence of regression by 5 years of age, the diagnosis of Rett syndrome should be questioned.

Clinical Efficacy
The efficacy of Daybue was evaluated in one pivotal trial called LAVENDER that assessed Daybue in female patients 5 to 20 years of age with Rett syndrome.[6] Evidence for effectiveness in patients 2 to 4 years of age with Rett syndrome was provided by a bridging pharmacokinetic study, DAFFODIL.[7] For each of these studies, patients were enrolled if they had a diagnosis of typical Rett syndrome, according to the Rett syndrome diagnostic criteria, with a documented disease-causing mutation in the *MECP2* gene, and were post-regression status for ≥ 6 months at screening (i.e., no loss or degradation in ambulation, hand function, speech, nonverbal communicative or social skills).[6,7] Daybue has been evaluated for up to 40 weeks in LILAC, a published, open-label extension study of the 12-week, placebo-controlled LAVENDER study in

patients with Rett syndrome, and for up to 32 months in LILAC-2, a published, open-label extension study of LILAC.[8,9] LILAC enrolled 154 patients who had completed LAVENDER and LILAC-2 enrolled 77 patients who had completed LILAC.

Guidelines
A US expert consensus on real-world use of Daybue in Rett syndrome is available (2025)[10]. Per the consensus, Daybue should be part of standard of care for Rett syndrome in patients ≥ 2 years of age, as indicated (88% agreement) and may be given at any time throughout the patient's lifetime as indicated (100% agreement). Daybue may improve a patient's attention and (nonverbal and verbal) communication within one month of initiation (92% agreement) and fine and gross motor skills, hand use, hyperventilation, altered breathing patterns, bruxism, sleep patterns, anxiety, and irritability as early as three months after initiation (84% agreement). Patients should receive Daybue for 6 months after titrating to their weight-banded, or highest tolerable, dose to properly assess the efficacy of treatment (96% agreement). Documentation of improvements on Daybue should be mainly based on caregiver and/or clinician observations, rather than the exclusive use of specific assessments (Clinical Global Impression-Improvement or Rett Syndrome Behavior Questionnaire), as not all improvements can be captured by these assessments (96% agreement).

Coverage Policy

POLICY STATEMENT
Prior Authorization is required for benefit coverage of Daybue. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Daybue as well as the monitoring required for adverse events and long-term efficacy, approval requires Daybue to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Documentation: Documentation is required where noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, laboratory tests, claims records, prescription receipts and/or other information. All documentation must include patient-specific identifying information.

Daybue is considered medically necessary when the following criteria are met:

FDA-Approved Indication

1. **Rett Syndrome.** Approve for the duration noted if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy. Approve for 6 months if the patient meets the following criteria (i, ii, iii, iv, and v):
     - **i.** Patient is ≥ 2 years of age; AND
     - **ii.** Patient has a pathogenic variant in the *MECP2* gene **[documentation required]**; AND
     - **iii.** Patient has classic/typical Rett Syndrome, according to the Rett Syndrome Diagnostic Criteria **[documentation required]**; AND
       Note: The diagnosis of classic/typical Rett syndrome requires all main diagnostic criteria and none of the exclusion criteria. The main Rett syndrome diagnostic criteria are: 1) partial or complete loss of acquired purposeful hand skills; 2) partial or complete loss of acquired spoken language; 3) gait abnormalities, i.e., impaired (dyspraxic) or absence of ability; and 4) stereotypic hand movements, such as hand

wringing/squeezing, clapping/tapping, mouthing and washing/rubbing automatisms. The exclusion criteria for classic/typical Rett syndrome are: 1) brain injury secondary to trauma (peri- or postnatally), neurometabolic disease, or severe infection that causes neurological problems; and 2) grossly abnormal psychomotor development in first 6 months of life.

iv. According to the prescriber, the patient is past the initial period of regression; AND
Note: Being past the initial period of regression is defined as no additional loss or degradation in ambulation, hand function, speech, or nonverbal communicative or social skills within 6 months of initial period of regression.

v. The medication is prescribed by or in consultation with a neurologist; OR

B) Patient is Currently Receiving Daybue. Approve for 1 year if the patient meets BOTH of the following (i and ii):

i. Patient has been receiving Daybue for at least 6 months; AND
Note: If patient has taken Daybue for < 6 months use criterion A (Initial Therapy).

ii. According to the prescriber, patient has demonstrated a meaningful response to therapy.
Note: Examples of a meaningful response to therapy include improvements in attention, nonverbal or verbal communication, fine or gross motor skills, hand use, hyperventilation, altered breathing patterns, bruxism, sleep patterns, anxiety, or irritability.

Conditions Not Covered

Daybue for any other use is considered not medically necessary. Criteria will be updated as new published data are available.

References

1. Daybue® oral solution and Daybue® Stix powder for oral solution [prescribing information]. San Diego, CA: Acadia; December 2025.
2. National Institute of Neurological Disorders and Stroke. Rett syndrome. Last updated on April 7, 2025. Available at: https://www.ninds.nih.gov/health-information/disorders/rett-syndrome. Accessed on February 10, 2026.
3. International Rett Syndrome Foundation. What is Rett syndrome? Available at: https://www.rettsyndrome.org/about-rett-syndrome/what-is-rett-syndrome/. Accessed on February 10, 2026.
4. Collins BE, Neul JL. Rett syndrome and MECP2 duplication syndrome: disorders of MeCP2 dosage. *Neuropsychiatr Dis Treat*. 2022;18:2813-2835.
5. Neul JL, Kaufmann WE, Glaze DG, et al.; RettSearch Consortium. Rett syndrome: revised diagnostic criteria and nomenclature. *Ann Neurol*. 2010;68(6):944-50.
6. Neul JL, Percy AK, Benke TA, et al. Trofinetide for the treatment of Rett syndrome: a randomized phase 3 study. *Nat Med*. 2023;29(6):1468-1475.
7. Center for Drug Evaluation and Research. Daybue clinical review. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2023/217026Orig1s000MedR.pdf. Accessed on February 10, 2026.
8. Percy AK, Neul JL, Benke TA, et al. Trofinetide for the treatment of Rett syndrome: Results from the open-label extension LILAC study. *Med*. 2024;5(9):1178-1189.

9. Percy AK, Neul JL, Benke TA, et al. Trofinetide for the treatment of Rett syndrome: Long-term safety and efficacy results of the 32-month, open-label LILAC-2 study. *Med*. 2024;5(10):1275-1281.
10. Prange E, Beisang A, Pehlivan D, et al. Expert consensus on real-world use of trofinetide for Rett syndrome using a modified Delphi method.

Revision Details

Summary of Changes	Review Date	Effective Date
Updated coverage policy title from *Trofinetide* to *Neurology – Daybue.*	5/3/2024	8/01/2024
Individual and Family plans added to the policy. **Added** a note defining the diagnostic criteria and exclusion criteria for classic/typical Rett syndrome. **Updated** the requirement for a patient to be "past the initial period of regression" to "past the initial period of regression and has reached the plateau phase" **Reworded** the conditions not covered statement.	4/24/2025	6/15/2025
Product List: Daybue Stix added to policy. **Documentation Statement** updated **from** "Documentation is required where noted in the criteria. Documentation may include, but not limited to, chart notes, laboratory tests, claims records, and/or other information" **to** **"**Documentation is required where noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, laboratory tests, claims records, prescription receipts and/or other information. All documentation must include patient-specific identifying information." **Rett Syndrome:** **Initial Therapy:** Approval duration updated from 1 year to 6 months. **Updated from** "Documentation is provided of a pathogenic variant in the *MECP2* gene" **to** "Patient has a pathogenic variant in the *MECP2* gene **[documentation required]**" **Updated from** "Documentation is provided of classic/ typical Rett Syndrome, according to the Rett Syndrome Diagnostic Criteria" **to** "Patient has classic/typical Rett Syndrome, according to the Rett Syndrome Diagnostic Criteria **[documentation required]**" **Updated from "**According to the prescriber, the patient is past the initial period of regression and has reached the plateau phase (for example, no additional loss or degradation in ambulation, hand function, speech, or nonverbal communicative or social skills within 6 months of initial period of regression)" **to** "According to the prescriber, the patient is past the initial period of regression Note: Being past the initial period of regression is defined as no	4/30/2026	6/15/2026

additional loss or degradation in ambulation, hand function, speech, or nonverbal communicative or social skills within 6 months of initial period of regression” **Patient is Currently Receiving Daybue:** Criteria added to policy.		

The policy effective date is in force until updated or retired.

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