PRIOR AUTHORIZATION POLICY

POLICY: Neurology – Daybue Prior Authorization Policy
- Daybue™ (trofinetide oral solution – Acadia)

REVIEW DATE: 04/23/2025

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.

CIGNA NATIONAL FORMULARY COVERAGE:

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 mutation 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* mutations 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 current Daybue efficacy information is insufficient to determine if the medication demonstrates any clinically meaningful benefits.[6-10] In the absence of additional clinical trials, there is not enough information to support approval. The efficacy of Daybue was evaluated in one pivotal trial called LAVENDER that assessed Daybue in female patients with Rett syndrome.[6,7] Confirmatory evidence of efficacy was provided by RETT-002, a non-pivotal, dose-ranging trial that evaluated Daybue in female patients with Rett syndrome.[8] 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).[6-8] 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.[9,10] LILAC enrolled 154 patients who had completed LAVENDER and LILAC-2 enrolled 77 patients who had completed LILAC.

POLICY STATEMENT

Due to the lack of clinical efficacy data and safety concerns, **approval is not recommended** for Daybue. The current Daybue efficacy information is insufficient to determine if the medication demonstrates any clinically meaningful benefits. In the absence of additional clinical trials, there is not enough information to support approval.

CONDITIONS NOT COVERED

- **Daybue™ (trofinetide oral solution - Acadia)**

is(are) considered not medically necessary for ANY use(s) including the following (this list may not be all inclusive; criteria will be updated as new published data are available):

1. **Rett Syndrome.** The efficacy of Daybue was evaluated in one pivotal trial called LAVENDER that assessed Daybue in female patients with Rett syndrome.[6,7] A non-pivotal, dose-ranging trial, RETT-002, also evaluated Daybue in female patients with Rett syndrome.[8] Evidence for use 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).[6-8] After 12 weeks, LAVENDER demonstrated marginal efficacy on the subjective co-primary efficacy endpoints of the Rett Syndrome Behaviour Questionnaire (RSBQ) [the scale ranges from 0 to 90] and the Clinical Global Impression-Improvement (CGI-I) score (scale ranges from 0 to 7).[6,7] The open-label extension studies (LILAC [up to 40 weeks on therapy] and LILAC-2 [up to 32 months on therapy]) continued to demonstrate marginal clinical efficacy on the RSBQ and CGI-I scores and continued high rates of diarrhea and vomiting.[9,10]

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

REFERENCES

1. Daybue™ oral solution [prescribing information]. San Diego, CA: Acadia; September 2024.
2. National Institute of Neurological Disorders and Stroke. Rett syndrome. Last updated on November 28, 2023. Available at: https://www.ninds.nih.gov/health-information/disorders/rett-syndrome. Accessed on April 17, 2025.
3. International Rett Syndrome Foundation. What is Rett syndrome? Available at: https://www.rettsyndrome.org/about-rett-syndrome/what-is-rett-syndrome/. Accessed on April 17, 2025.
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 April 17, 2025.

8. Gaze DG, Neul JL, Kaufmann WE, et al. Double-blind, randomized, placebo-controlled study of trofinetide in pediatric Rett syndrome. *Neurology*. 2019;92:e1912-e1925.
9. 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.
10. 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.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	04/12/2023
Selected Revision	**Rett Syndrome:** This condition was moved from the Recommended Authorization Criteria to the Conditions Not Covered because the current Daybue efficacy information is insufficient to determine if the medication demonstrates any clinically meaningful benefits. In the absence of additional clinical trials, there is not enough information to support approval.	05/24/2023
Annual Revision	No criteria changes.	04/19/2024
Annual Revision	No criteria changes.	04/23/2025