PRIOR AUTHORIZATION POLICY

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

REVIEW DATE: 04/19/2024

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.[6-8] 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]

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.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

None.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Daybue is not recommended in the following situations:

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]

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

REFERENCES

1. Daybue™ oral solution [prescribing information]. San Diego, CA: Acadia; March 2023.
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 15, 2024.
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 15, 2024.
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 15, 2024.
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.