Original Effective Date: 08/30/2023
Current Effective Date: 06/11/2026
Last P&T Approval/Version: 04/29/2026
Next Review Due By: 04/2027
Policy Number: C25469-A

Daybue (trofinetide)

PRODUCTS AFFECTED

Daybue (trofinetide)

COVERAGE POLICY

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Coverage Guideline must be read in its entirety to determine coverage eligibility, if any. This Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide Molina Healthcare complete medical rationale when requesting any exceptions to these guidelines.

Documentation Requirements:
Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

DIAGNOSIS:
Rett syndrome

REQUIRED MEDICAL INFORMATION:
This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. This clinical policy will be reviewed along with state and federal requirements, the benefit being administered, and formulary preferencing. If a drug within this policy receives an updated FDA label within the last 180 days, medical necessity for the member will be reviewed using the updated FDA label information. Coverage will be determined on a case-by-case basis until the criteria can be updated through Molina Healthcare, Inc. clinical governance. Additional information may be required on a case-by-case basis to allow for adequate review. When the requested drug product for coverage is dosed by weight, body surface area or other member specific measurement, this data element is required as part of the medical necessity review. The Pharmacy and Therapeutics Committee has determined that the drug benefit shall be a mandatory generic and that generic drugs will be dispensed whenever available. The Pharmacy and Therapeutics Committee has determined that biosimilars may be preferred.

A. RETT SYNDROME:
   1. Documentation of diagnosis of classical or typical Rett Syndrome (RTT)
      AND
   2. Documentation that the member has mutation of the MECP2 gene [DOCUMENTATION

REQUIRED]
AND

3. Documentation that the member's weight is at least 9 kilograms
AND
4. Documentation of ONE of the following RTT clinical scores at baseline [DOCUMENTATION REQUIRED]
   a) Rett Syndrome Behaviour Questionnaire (RSBQ) total score
   Note: RSBQ is a caregiver-completed rating scale assessing 45 items and having a maximum score of 90. Lower scores reflect lesser severity in signs and symptoms of Rett syndrome.
   OR
   b) Clinical Global Impression Severity (CGI-S) score of 4 or greater
   Note: The Clinical Global Impression (CGI) has two components. The CGI-Severity is completed by the clinician to rate severity of illness. The Clinical Global Impression Improvement (CGI-I) is used to rate the change from baseline due to treatment.
   AND
5. Documentation by prescriber of member baseline signs and symptoms (e.g., hand skills and movements, speech, gait, etc.)

CONTINUATION OF THERAPY:

A. RETT SYNDROME:

1. Documentation of positive clinical response as improvement from baseline in ONE of the following [DOCUMENTATION REQUIRED]
   a) Reduction in the Rett Syndrome Behaviour Questionnaire (RSBQ) total score
   OR
   b) Reduction in the Clinical Global Impression Severity (CGI-S) score
   Note: CGI-S is a 7-point scale ranging from 1=normal to 7=among the most extremely ill patients
   OR
   c) Clinical Global Impression Improvement (CGI-I) score of less than 4
   Note: CGI-I is 7-point scale completed by clinicians with 1=very much improved to 7=very much worse. A score of 4= no change from baseline.
   OR
   d) Other prescriber documentation of improvement in the condition's signs and symptoms (e.g., hand skills and movements, speech, gait, etc.)
   AND
2. Prescriber attests to or clinical reviewer has found no evidence of intolerable adverse effects or drug toxicity
   MOLINA REVIEWER NOTE: If diarrhea or weight loss, refer to FDA labeled guidance

DURATION OF APPROVAL:

Initial authorization: 12 months, Continuation of Therapy: 12 months

PRESCRIBER REQUIREMENTS:

Prescribed by or in consultation with a neurologist or physician experienced in the management of Rett Syndrome. [If prescribed in consultation, consultation notes must be submitted with initial request and reauthorization requests]

AGE RESTRICTIONS:

2 years of age and older

QUANTITY:

Member Weight	Recommended Dosage	Recommended Oral Solution Volume
9 kg to <12 kg	5,000 mg twice daily	25 mL twice daily
12 kg to <20 kg	6,000 mg twice daily	30 mL twice daily
20 kg to <35 kg	8,000 mg twice daily	40 mL twice daily
35 kg to <50 kg	10,000 mg twice daily	50 mL twice daily
50 kg or greater	12,000 mg twice daily	60 mL twice daily

PLACE OF ADMINISTRATION:
The recommendation is that oral medications in this policy will be for pharmacy benefit coverage and patient self-administered.

DRUG INFORMATION

ROUTE OF ADMINISTRATION:
Oral

DRUG CLASS:
Rett Syndrome Agents – Glycine-Proline-Glutamate Analogs

FDA-APPROVED USES:
Indicated for the treatment of Rett syndrome in adults and pediatric patients 2 years of age and older

COMPENDIAL APPROVED OFF-LABELED USES:
None

APPENDIX

APPENDIX:
Diagnostic Criteria for Typical or Classic RTT

Required	1. A period of regression followed by recovery or stabilization 2. All main criteria and all exclusion criteria 3. Supportive criteria are not required, although often present in typical RTT
Main criteria	1. Partial or complete loss of acquired purposeful hand skills 2. Partial or complete loss of acquired spoken language 3. Gait abnormalities: Impaired (dyspraxic) or absence of ability 4. Stereotypic hand movements such as hand wringing/squeezing, clapping/tapping, mouthing, and washing/rubbing automatisms
Exclusion criteria	1. Brain injury secondary to trauma (peri- or postnatally), neurometabolic disease, or severe infection that causes neurological problems 2. Grossly abnormal psychomotor development in the first 6 months of life

RTT Stages

Stage	Age	Signs and Symptoms
Early onset	6-18 months	Growth and development slow or stop; potential delays in motor functions
Rapid deterioration	1-4 years	Loss of abilities that children previously had including communication, social, and motor skills; breathing and coordination problems can begin
Plateau	2-10 years	Previous symptoms may slow or improve slightly; seizures and cardiac arrhythmias may develop
Late motor deterioration	10 years and older	Muscle weakness, reduced mobility, and potential scoliosis; Communication skills can remain stable

BACKGROUND AND OTHER CONSIDERATIONS

BACKGROUND:
Rett syndrome (RTT) is a neurodevelopmental disorder that is caused by X chromosome mutations on the MECP2 gene. RTT is a rare, X-linked, genetic disorder that impacts mainly females, but a few cases have been reported in males. About 1 in 10,000 to 15,000 live female births are impacted by RTT. The symptoms of the disorder typical arise when the child is between 1 and 4 years old. Central nervous system (CNS) impairment is the characteristic sign of RTT. Symptoms have a wide range in severity and can include changes in gait, partial loss of hand use and expressive language, and hand movements such as wringing, clapping, or rubbing. Several other symptoms that patients can present with include seizures, respiratory complications, gastrointestinal issues, and disruptive or anxiety behaviors.

Daybue was the first treatment for RTT to receive FDA-approval. The standard of care for this condition is symptom management, with medications and non-pharmacologic options. Occupational and physical therapy may also be recommended as supportive therapy.

The efficacy and safety of Daybue were evaluated in the Phase 3 LAVENDER study, a 12-week, double-blind, randomized, placebo-controlled study. There were 187 female participants 5 to 20 years of age with typical or classic RTT. The co-primary endpoints were the Rett Syndrome Behaviour Questionnaire (RSBQ) and the Clinical Global Impression-Improvement (CGI-I) assessment. The RSBQ is a caregiver assessment that scores symptoms of RTT with a lower score meaning less severe disease. Key inclusion criteria in the LAVENDER study required a RSBQ rating of 10-36 and a CGI-S score of greater than over equal to 4. The Daybue to placebo difference after 12 weeks of treatment was -3.2 (p=0.018, 95% CI -5.7,
-6.0). The CGI-I is an assessment administered by clinicians to determine if a patient has improved after treatment with a decrease representing an improvement. The Daybue to placebo difference after 12 weeks of treatment was -0.3 (p=0.003, 95% CI -0.5, -0.1). An analysis of CGI-I scores was also conducted, which revealed that 61% of patients in the Daybue group had no change in RTT symptoms, while 24.7% had minimal improvement and 13% were much improved. In the placebo group, 81.4% of patients had no change, 10.5% were minimally improved, and 4.7% were much improved. The study discontinuation rate of Daybue due to adverse effects was 19%, with 15% attributed to diarrhea. The most common adverse reactions to Daybue treatment were diarrhea and vomiting. Over 95% of these reactions were classified as mild to moderate.

CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION:
All other uses of Daybue (trofinetide) are considered experimental/investigational and therefore, will follow Molina's Off- Label policy. Contraindications to Daybue (trofinetide) include: No labeled contraindications.

OTHER SPECIAL CONSIDERATIONS:
Daybue (trofinetide) oral solution should be stored in an upright position and refrigerated (36°F to 46°F). The oral solution should be discarded after 14 days of first opening of the bottle.

If vomiting occurs after Daybue administration, an additional dose should not be taken. Instead, continue with the next scheduled dose. Interrupt, reduce dose, or discontinue Daybue if vomiting is severe or occurs despite medical management.

CODING/BILLING INFORMATION

CODING DISCLAIMER. *Codes listed in this policy are for reference purposes only and may not be all-inclusive or applicable for every state or line of business. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement. Listing of a service or device code in this policy does not guarantee coverage. Coverage is determined by the benefit document. Molina adheres to Current Procedural Terminology (CPT®), a registered trademark of the American Medical Association (AMA). All CPT codes and descriptions are copyrighted by the AMA; this information is included for informational purposes only. Providers and facilities are expected to utilize industry-standard coding practices for all submissions. Molina has the right to reject/deny the claim and recover claim payment(s) if it is determined it is not billed appropriately or not a covered benefit. Molina reserves the right to revise this policy as needed.*

HCPCS CODE	DESCRIPTION
NA	

AVAILABLE DOSAGE FORMS:
Daybue SOLN 200MG/ML
Daybue Stix PACK 5000MG, 6000MG, 8000MG

REFERENCES

1. Daybue (trofinetide) oral solution; for oral solution [prescribing information]. San Diego, CA: Acadia Pharmaceuticals, Inc.; March 2026.
2. Fu C, Armstrong D, Marsh E, et al. Consensus guidelines on managing Rett syndrome across the lifespan BMJ Paediatrics Open 2020;4:e000717. doi: 10.1136/bmjpo-2020-000717.
3. Glaze DG, et al. A double-blind, randomized, placebo-controlled clinical study of trofinetide in the treatment of Rett syndrome. Pediatr Neurol. 2017;76:37–46. doi:10.1016/j.pediatrneurol.2017.07.002
4. Glaze DG, et al. Double-blind, randomized, placebo-controlled study of trofinetide in pediatric Rett syndrome. Neurology. 2019;92(16):e1912–e1925. doi:10.1212/WNL.0000000000007316
5. Primary Care Guidelines. Retrieved May 8, 2023, from https://www.rettsyndrome.org/wp-content/uploads/IRSF_PrimaryCareGdlns_REV2021.pdf.
6. Neul, J. L., Percy, A. K., Benke, T. A., Berry-Kravis, E. M., Glaze, D. G., Peters, S. U., Jones, N. E., & Youakim, J. M. (2022). Design and outcome measures of LAVENDER, a phase 3 study of trofinetide for Rett syndrome. Contemporary clinical trials, 114, 106704. https://doi.org/10.1016/j.cct.2022.106704.
7. Neul, J. L., Kaufmann, W. E., Glaze, D. G., Christodoulou, J., Clarke, A. J., Bahi-Buisson, N., Leonard, H., Bailey, M. E. S., Schanen, N. C., Zappella, M., Renieri, A., Huppke, P., & Percy, A. K. (2010). Rett syndrome: Revised diagnostic criteria and nomenclature. Annals of Neurology, 68(6), 944–950. https://doi.org/10.1002/ana.22124
8. Busner, J., & Targum, S. D. (2007). The clinical global impressions scale: applying a research tool in clinical practice. Psychiatry (Edgmont (Pa.: Township)), 4(7), 28–37.

SUMMARY OF REVIEW/REVISIONS	DATE
REVISION- Notable revisions: Required Medical Information Available Dosage Forms References	Q2 2026
REVISION- Notable revisions: Duration of Approval Prescriber Requirements Other Special Considerations References	Q2 2025
REVISION- Notable revisions: Required Medical Information Continuation of Therapy Drug Class Contraindications/Exclusions/Discontinuation	Q2 2024
NEW CRITERIA CREATION	Q3 2023