Clinical Policy: Trofineatide (Daybue)

Reference Number: PA.CP.PHAR.600
Effective Date: 06/2023
Last Review Date: 05/2023

Description
Trofinetide (Daybue™) is an insulin-like growth factor 1 (IGF-1) analog.

FDA Approved Indication(s)
Daybue is indicated for the treatment of Rett syndrome (RTT) in adults and pediatric patients 2 years of age and older.

Policy/Criteria
Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

It is the policy of PA Health & Wellness® that Daybue is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Rett Syndrome (must meet all)**:**

1. Diagnosis of RTT with both of the following (a and b):
   a. Classic/typical RTT (*see Appendix D*);
   b. *MECP2* gene mutation confirmed by genetic testing;
2. Prescribed by or in consultation with a pediatric neurologist, geneticist, or developmental pediatrician;
3. Age ≥ 2 years;
4. Weight ≥ 9 kg;
5. Member has had no seizures or has a stable pattern of seizures (e.g., no changes in seizure frequency, antiepileptic drugs, or behavioral treatments);
6. Documentation of one of the following baseline assessment scores (a or b):
   a. Rett Syndrome Behavior Questionnaire (RSBQ) (*see Appendix E*);
   b. Clinical Global Impression-Severity (CGI-S) of ≥ 4 (*see Appendix F*);
7. At the time of request, member does not have either of the following (a and b):
   a. Long QT syndrome or baseline QTcF interval > 450 msec;
   b. Current treatment with insulin;
8. Dose does not exceed any of the following (a, b, c, d, or e):
   a. Weight 9 kg to < 12 kg: 10,000 mg (50 mL) per day;
   b. Weight 12 kg to < 20 kg: 12,000 mg (60 mL) per day;
   c. Weight 20 kg to < 35 kg: 16,000 mg (80 mL) per day;
   d. Weight 35 kg to < 50 kg: 20,000 mg (100 mL) per day;
   e. Weight ≥ 50 kg: 24,000 mg (120 mL) per day.

Approval duration: 6 months

B. Other diagnoses/indications

1. Refer to the off-label use policy if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): PA.CP.PMN.53

II. Continued Therapy

A. Rett Syndrome (must meet all)**:**

1. Currently receiving medication via PA Health & Wellness benefit and documentation supports positive response to therapy or the Continuity of Care policy (PA.LTSS.PHAR.01) applies;
2. Member is responding positively to therapy as evidenced by, including but not limited to, improvement in any of the following parameters (a, b, or c):
   a. ≥ 3 point reduction in overall RSBQ total score from baseline;
   b. If the member has received Daybue for 6 months or less, they currently must have a CGI-I score between 1-4;
   c. If the member has received Daybue for more than 6 months, they currently must have a CGI-I score between 1-3;
3. If request is for a dose increase, new does not exceed any of the following (a, b, c, d, or e):
   a. Weight 9 kg to < 12 kg: 10,000 mg (50 mL) per day;
   b. Weight 12 kg to < 20 kg: 12,000 mg (60 mL) per day;
   c. Weight 20 kg to < 35 kg: 16,000 mg (80 mL) per day;
   d. Weight 35 kg to < 50 kg: 20,000 mg (100 mL) per day;
   e. Weight ≥ 50 kg: 24,000 mg (120 mL) per day.

   Approval duration: 6 months

B. Other diagnoses/indications (must meet 1 or 2)**:**

1. Currently receiving medication via PA Health & Wellness benefit and documentation supports positive response to therapy or the Continuity of Care policy (PA.LTSS.PHAR.01) applies.
   Approval duration: Duration of request or 12 months (whichever is less); or
2. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): PA.CP.PMN.53

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policies – PA.CP.PMN.53

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

CGI-I: Clinical Global Impression-Improvement
CGI-S: Clinical Global Impression-Severity
FDA: Food and Drug Administration
IGF-1: insulin-like growth factor 1
RSBQ: Rett Syndrome Behavior Questionnaire
RTT: Rett syndrome

Appendix B: Therapeutic Alternatives
Not applicable

Appendix C: Contraindications/Boxed Warnings
None reported

Appendix D: General Information
- RTT is a rare neurodevelopment disorder that occurs almost exclusively in females; however, there have been cases seen in males.
- Mutations on the *MECP2* gene occur in 90-95% of RTT cases.
  - The *MECP2* gene is imperative for the normal functioning of nerve cells.
- According to the International Rett Syndrome Foundation, classical/typical RTT is defined by these criteria:
  - Main criteria
    - Partial or complete loss of acquired purposeful hand skills
    - Partial or complete loss of acquired spoken language
    - Gait abnormalities: impaired or absence of ability to walk
    - Hand wringing/squeezing/clapping, mouthing, and/or washing/rubbing that seems habitual or uncontrollable (stereotypical of RTT)
  - Exclusion criteria
    - Brain injury secondary to trauma, neurometabolic disease, or severe infection that causes neurological problems
    - Grossly abnormal psychomotor development in the first 6 months of life
  - Supportive criteria
    - Breathing disturbances when awake, bruxism when awake, abnormal muscle tone, impaired sleep pattern, peripheral vasomotor disturbances, scoliosis/kyphosis, growth retardation, small cold hands and feet, inappropriate laughing/screaming spells, diminished response to pain, intense eye communication-use of eye pointing
  - Required criteria for classical RTT
    - A period of regression followed by recovery or stabilization
    - All main criteria and all exclusion criteria
    - Supportive criteria are not required, though often present in typical RTT
- Individuals with RTT may also suffer from seizures, autism, cardiovascular dysfunction, and gastrointestinal issues, often requiring a gastrostomy tube.

Appendix E: Rett Syndrome Behavior Questionnaire (RSBQ)
The RSBQ is used to assess characteristics of RTT. It consists of 45 questions across eight categories, each question with three answers at values of 0, 1, and 2; 0 corresponds to "never", 1 to "sometimes", and 2 to "always".

RSBQ Category
General mood
Breathing problems
Hand behaviors
Repetitive face movements

RSBQ Category
Body rocking and expressionless face
Night-time behaviors
Fear/anxiety
Walking/standing
Total (Max Score = 90)

Appendix F: Clinical Global Impression Score
Score rated on a 7-point scale used to determine if illness was improved or worsened.

CGI-S	CGI-I	Score
Normal	Very much improvement	1
Borderline ill	Much improved	2
Mildly ill	Minimally improved	3
Moderately ill	No change	4
Markedly ill	Minimally worse	5
Severely ill	Much worse	6
Extremely ill	Very much worse	7

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
RTT	Dose can be given orally or via gastrostomy (G) tube or gastrojejunal tube a. Weight 9 kg to < 12 kg: 5,000 mg (25 mL) twice daily b. Weight 12 kg to < 20 kg: 6,000 mg (30 mL) twice daily c. Weight 20 kg to < 35 kg: 8,000 mg (40 mL) twice daily d. Weight 35 kg to < 50 kg: 10,000 mg (50 mL) twice daily e. Weight ≥ 50 kg: 12,000 mg (60 mL) twice daily	24,000 mg/day

VI. Product Availability

Oral solution: 200 mg/ml

VII. References

1. Daybue Prescribing Information. San Diego, CA: Acadia Pharmaceuticals Inc.; March 2023. Available at: https://acadia.com/wp-content/uploads/2023/03/daybue-prescribing-information.pdf. Accessed March 23, 2023.
2. Neul JL, Percy AK, Benke TA, et al. Design and outcome measures of Lavender, a phase 3 study of trofinetide for Rett Syndrome. Contemporary Clinical Trials. 2022;114:106704. doi:10.1016/j.cct.2022.106704.

3. Neul JL, Glaze DG, Percy AK, et al. Improving treatment trial outcomes for Rett syndrome: the development of Rett-specific anchors for the Clinical Global Impression scale. J Child Neurol. 2015;30(13):1743-1748. doi:10.1177/0883073815579707.
4. Busner J, Targum SD. The Clinical Global Impressions scale: applying a research tool in clinical practice. Psychiatry (Edgmont). 2007;4(7):28-37.
5. Cianfaglione R, Clarke A, Kerr M, et al. A national survey of Rett syndrome: behavioural characteristics. J Neurodevelop Disord. 2015;7(1):11.
6. ClinicalTrials.gov. Study of trofinetide for the treatment of girls and women with Rett Syndrome (LAVENDER™). Available at: https://clinicaltrials.gov/ct2/show/study/NCT04181723. Accessed September 26, 2022.
7. Glaze DG, Neul JL, Kaufmann WE, 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.
8. Fu C, Armstrong D, Marsh E, et al. Consensus guidelines on managing Rett syndrome across the lifespan. BMJ Paediatr Open. Sep 2020;4(1):e000717.
9. Mount RH, Charman T, Hastings RP, et al. The Rett Syndrome Behaviour Questionnaire (RSBQ): refining the behavioural phenotype of Rett syndrome. Journal of Child Psychology and Psychiatry. 2002;43(8):1099-1110.
10. Rett syndrome diagnosis. Rettsyndrome.org. Available at: https://www.rettsyndrome.org/about-rett-syndrome/rett-syndrome-diagnosis/. Accessed September 29, 2022.
11. NORD (National Organization for Rare Disorders). Rett syndrome. Published 2015. Available at: https://rarediseases.org/rare-diseases/rett-syndrome/. Accessed September 29, 2022.
12. NIH.gov. Rett syndrome | Genetic and Rare Diseases Information Center (GARD) – an NCATS Program. Published 2014. Available at: https://rarediseases.info.nih.gov/diseases/5696/rett-syndrome. Accessed September 29, 2022.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created	05/2023	