Clinical Policy: Trofinetide (Daybue)

Reference Number: CP.PHAR.600
Effective Date: 03.10.23
Last Review Date: 05.23
Line of Business: Commercial, HIM, Medicaid

Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

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 health plans affiliated with Centene Corporation® 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 (must meet 1 or 2)**:**

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

II. Continued Therapy

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

1. Member meets one of the following (a or b):
   a. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
   b. Member is currently receiving medication and is enrolled in a state and product with continuity of care regulations (refer to state specific addendums for CC.PHARM.03A and CC.PHARM.03B);
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. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

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 – CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid, or evidence of coverage documents.

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
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

CGI-S	CGI-I	Score
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 • Weight 9 kg to < 12 kg: 5,000 mg (25 mL) twice daily • Weight 12 kg to < 20 kg: 6,000 mg (30 mL) twice daily • Weight 20 kg to < 35 kg: 8,000 mg (40 mL) twice daily • Weight 35 kg to < 50 kg: 10,000 mg (50 mL) twice daily • Weight ≥ 50 kg: 12,000 mg (60 mL) twice daily	24,000 mg/day

VI. Product Availability

Oral solution: 200 mg/mL

VII. References

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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.
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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.
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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.
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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 pre-emptively.	10.11.22	11.22
RT4: Drug is now FDA approved - policy updated per FDA labeling and clinical trial inclusion and exclusion criteria; requirement for CGI-I in the Initial Approval Criteria section was updated to CGI-S with the requirement for a minimum score of 4 to determine moderate disease severity; for Continued Therapy, added requirement for documentation of response to therapy via specific score improvements on the RSBQ or CGI-I; references reviewed and updated.	03.27.23	05.23

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

Note:
For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.