09-J4000-52

Original Effective Date: 07/01/23

Reviewed: 09/11/24

Revised: 10/15/24

Subject: Trofinetide (Daybue®) Oral Solution

THIS MEDICAL COVERAGE GUIDELINE IS NOT AN AUTHORIZATION, CERTIFICATION, EXPLANATION OF BENEFITS, OR A GUARANTEE OF PAYMENT, NOR DOES IT SUBSTITUTE FOR OR CONSTITUTE MEDICAL ADVICE. ALL MEDICAL DECISIONS ARE SOLELY THE RESPONSIBILITY OF THE PATIENT AND PHYSICIAN. BENEFITS ARE DETERMINED BY THE GROUP CONTRACT, MEMBER BENEFIT BOOKLET, AND/OR INDIVIDUAL SUBSCRIBER CERTIFICATE IN EFFECT AT THE TIME SERVICES WERE RENDERED. THIS MEDICAL COVERAGE GUIDELINE APPLIES TO ALL LINES OF BUSINESS UNLESS OTHERWISE NOTED IN THE PROGRAM EXCEPTIONS SECTION.

Dosage/ Administration	Position Statement	Billing/Coding	Reimbursement	Program Exceptions	Definitions
Related Guidelines	Other	References	Updates		

DESCRIPTION:

Rett syndrome is a neurodevelopmental disorder caused by a spontaneous mutation in the methyl CpG binding protein 2 (MECP2) gene. The MECP2 gene is needed for brain development to activate and deactivate gene functions. The disorder occurs most commonly in females and affects 1 in 10,000 girls under age 12. Developmental regression is the most pronounced between 1 and 4 years of age where children lose previously acquired motor, communication, and social skills followed by a plateau phase. Classic or typical diagnostic criteria includes a period of regression followed by recovery or stabilization with partial or complete loss of acquired purposeful hand skills, partial or complete loss of spoken language, gait abnormalities, and repetitive hand movements such as hand wringing/squeezing, clapping/tapping, mouthing, and washing/rubbing. Trofinetide is the first Food and Drug Administration (FDA) approved treatment for Rett syndrome in adults and pediatric patients 2 years of age and older. Trofinetide is a synthetic analog of the natural occurring protein in the brain, glycine-proline-glutamate (GPE).

The efficacy of trofinetide was evaluated in a randomized, double-blind, placebo-controlled trial over 12 weeks in patients diagnosed with Rett syndrome. Patients had a disease-causing mutation in the MECP2 gene and were 5 to 20 years of age. The efficacy was evaluated by a change from baseline after 12 weeks of treatment in the total score of the Rett Syndrome Behavior Questionnaire (RSBQ) (90-point scale completed by the caregiver) and the Clinical Global Impression-Improvement (CGI-I) score (7-point scale rated by the clinician). A reduction in the RSBQ indicates less severity in signs and symptoms of Rett syndrome (breathing, hand movements, repetitive behaviors, vocalizations, facial expressions, eye gaze, and mood). A reduction in the CGI-I also indicates improvement. Treatment with trofinetide demonstrated a statistically significant difference as compared to placebo in the change from baseline in RSBQ (-4.9 vs -1.7, p-value 0.018) and the CGI-I score (3.5 vs 3.8, p-value= 0.003) at week 12. The most common adverse reactions were diarrhea and vomiting.

POSITION STATEMENT:

Comparative Effectiveness

The FDA has deemed the drug(s) or biological product(s) in this coverage policy to be appropriate for self-administration or administration by a caregiver (i.e., not a healthcare professional). Therefore, coverage (i.e., administration) in a provider-administered setting such as an outpatient hospital, ambulatory surgical suite, physician office, or emergency facility is not considered medically necessary.

Initiation of trofinetide (Daybue) **meets the definition of medical necessity** when **ALL** the following criteria are met:

1. Rett syndrome
    a. Member has a diagnosis of typical (classic) Rett syndrome.
    b. Member's diagnosis is confirmed by a genetic mutation in the MECP2 gene – lab documentation must be submitted.
    c. Baseline assessment of the member's functional status using the Rett Syndrome Behavior Questionnaire (RSBQ) or the Clinical Global Impression-Improvement (CGI-I) score – documentation must be submitted
    d. The daily dose does not exceed weight-based dosing in Table 1.

Approval duration: 6 months

Continuation of trofinetide (Daybue) **meets the definition of medical necessity** when **ALL** the following criteria are met:

1. An authorization or reauthorization for trofinetide has been previously approved by Florida Blue or another health plan in the past 2 years for the treatment of Rett syndrome (if another health plan, documentation of a paid claim during the 90 days before the authorization request must be submitted), **OR** the member has previously met **ALL** indication-specific criteria.
2. The member has a beneficial response to treatment (historical improvement of the RSBQ or CGI-I score from baseline) – documentation must be submitted
3. The daily dose does not exceed weight-based dosing in Table 1.

Approval duration: 12 months

Table 1: Trofenitide dosing

Patient weight	Dosage	Volume
9 kg to less than 12 kg	5000 mg twice daily	25 mL twice daily
12 kg to less than 20 kg	6000 mg twice daily	30 mL twice daily
20 kg to less than 35 kg	8000 mg twice daily	40 mL twice daily
35 kg to less than 50 kg	10000 mg twice daily	50 mL twice daily
50 kg or more	12000 mg twice daily	60 mL twice daily

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved

Trofinetide is indicated for Rett Syndrome in adults and pediatric patients 2 years of age and older. The recommended dosage is twice daily, morning and evening, according to patient weight. Can be given orally or via gastrostomy tube; doses administered via gastrojejunal tubes must be administered through the G-port. May be administered with or without food.

Patient weight	Dosage	Volume
9 kg to less than 12 kg	5000 mg twice daily	25 mL twice daily
12 kg to less than 20 kg	6000 mg twice daily	30 mL twice daily
20 kg to less than 35 kg	8000 mg twice daily	40 mL twice daily
35 kg to less than 50 kg	10000 mg twice daily	50 mL twice daily
50 kg or more	12000 mg twice daily	60 mL twice daily

Dose Adjustments

- Do not redose if a dose is missed.
- Do not redose after vomiting.
- Interrupt, reduce the dose, or discontinue if severe diarrhea occurs, if dehydration is suspected, or if significant weight loss occurs.
- Stop laxatives before initiating therapy.

Drug Availability

- 200 mg/mL solution

PRECAUTIONS:

Boxed Warning - none

Contraindications - none

Precautions/Warnings

- Diarrhea – most patients experience diarrhea with treatment and should stop laxatives prior to starting therapy. If diarrhea occurs, start antidiarrheal treatment, increase oral fluids, and notify the prescriber. Interrupt, reduce dose, or discontinue treatment if severe diarrhea occurs or if dehydration is suspected.
- Weight loss - Monitor weight and interrupt, reduce dose, or discontinue if significant weight loss occurs.

BILLING/CODING INFORMATION:

The following codes may be used to describe:

HCPCS Coding

J8499	Prescription drug, oral, non-chemotherapeutic, Not Otherwise Specified

ICD-10 Diagnosis Codes That Support Medical Necessity

F84.2	Rett's Syndrome

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Part D: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

Medicare Advantage: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline review date.

DEFINITIONS:

None

RELATED GUIDELINES:

None

OTHER:

Typical (Classic) Rett Syndrome Diagnostic Criteria (1,2,3)	
1	**A period of regression followed by recovery or stabilization**
2	**All main criteria present:** • Partial or complete loss of acquired purposeful hand skills • Partial or complete loss of acquired spoken language • Gait abnormalities: Impaired or absence of ability • Stereotypic hand movements such as hand wringing/squeezing, clapping/tapping, mouthing, and washing/rubbing automatisms
3	**Exclusion of the following:** • Brain injury secondary to trauma (peri- or postnatally), neurometabolic disease, or severe infection that causes neurological problems • Grossly abnormal psychomotor development in first 6 months of life

REFERENCES:

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3. Hauser RA, Factor SA, Marder SR et al. KINECT 3: A phase 3 randomized, double-blind, placebo-controlled trial of valbenazine for tardive dyskinesia. Am J Psychiatry 2017; 174: 476-484.
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5. Fu C, Armstrong D, Marsh E et al. Consensus guidelines on managing Rett syndrome across the lifespan. BMJ Paediatrics Open. 2020; 4: e000717.
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8. Orphan Drug Designations and Approval [Internet]. Silver Spring (MD): US Food and Drug Administration; 2024 [cited 2024 Aug 30]. Available from: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm/.

COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 09/11/24.

GUIDELINE UPDATE INFORMATION:

07/01/23	New Medical Coverage Guideline.
10/15/24	Review and revision to guideline; consisting of updating the documentation requirements and references.