trofinetide (Daybue™)

EOCCO POLICY

Policy Type:PA/SP Pharmacy Coverage Policy: EOCCO281

Description

Trofinetide (Daybue) is an insulin-like growth factor-1 (IGF-1) analogue, FDA-approved for the treatment of Rett syndrome (RTT) in adults and children 2 years of age and older. Trofinetide (Daybue) is administered orally or via a gastrostomy tube twice daily according to weight-based dosing.

Length of Authorization

- Initial: three months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
trofinetide (Daybue)	Rett syndrome (RTT)	200 mg/mL solution	*Weight based (see appendix table)*

Initial Evaluation

I. **Trofinetide (Daybue)** may be considered medically necessary when the following criteria are met:
   A. Member is 2 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with a provider experienced in the diagnosis and management of Rett syndrome (e.g., pediatrician, neurologist, geneticist); **AND**
   C. Documentation of member's weight within the last 3 months; **AND**
   D. Member has a diagnosis of **classic or typical Rett syndrome**; **AND**
      1. Diagnosis is confirmed by genetic testing that documents a mutation in *MECP2* gene; **AND**
      2. Provider attestation diagnosis is confirmed by ALL of the following clinical features of classic or typical RTT:
         i. Absence of grossly abnormal psychomotor development in first 6 months of life**; AND**
         ii. A period of regression followed by recovery or stabilization**; AND**
         iii. Partial or complete loss of acquired purposeful hand skills**; AND**
         iv. Partial or complete loss of acquired spoken language**; AND**
         v. Gait abnormalities: Impaired (dyspraxic) or absence of ability**; AND**
         vi. Stereotypic hand movements such as hand wringing/squeezing, clapping/tapping, mouthing and washing/rubbing automatisms**; AND**

vii. Absence of brain injury secondary to trauma (peri- or postnatally), neurometabolic disease, or severe infection that causes neurological problems

II. Trofinetide (Daybue) is considered investigational when used for all other conditions, including but not limited to:
   A. Pediatric patients less than 2 years of age
   B. Atypical or variant Rett syndrome (e.g., preserved speech (Zappella) variant, early onset seizures (Hanefeld) variant, and congenital (Rolando) variant)
   C. *MECP2*-mutation related disorders without clinical diagnostic symptoms of classic/typical Rett syndrome (e.g., *MECP2*-related severe neonatal encephalopathy, *PPMX*-syndrome, *MECP2* duplication syndrome)
   D. Other neurogenerative disorders or disorders that may have symptoms or physical features that are similar to Rett syndrome (e.g., autism spectrum disorder, encephalitis, spastic ataxia, cerebral palsy, spinocerebellar degeneration, leukodystrophies, neuroaxonal dystrophy)
   E. *CDKL5*-mutation disorders (e.g., infantile spasms, West syndrome, Lennox-Gastaut syndrome)
   F. Other metabolic or degenerative disorders (e.g., neuronal ceroid lipofuscinosis, phenylketonuria, and urea cycle disorders)
   G. *FOXG1*-mutation related disorders
   H. Pitt-Hopkins syndrome
   I. Angelman syndrome

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Documentation of member's weight within the last 3 months; **AND**
IV. Provider attestation that trofinetide (Daybue) continues to slow or stabilize the progression of disease and treatment provides clinical benefit to the member.

Supporting Evidence

I. Rett syndrome (RTT) is a progressive X-linked neurodevelopmental disorder that almost exclusively affects females. In the United States, approximately 11,000 patients are affected by RTT. Infants with RTT generally develop normally for about 6 to 18 months after birth, at which point regression of early milestones occurs. The ability to communicate, walk, and eat halt and begin to regress. Gradual deterioration continues into and throughout adulthood. Patients with RTT have a reduced life expectancy into the forties or fifties.

II. Common features associated with progression of the disorder include severe loss of language skills, fine and gross motor skills, dysphagia, seizures, breathing abnormalities, growth failure, bone mineral deficits (including fractures), autonomic nervous system dysfunction, cardiac abnormalities, and tone abnormalities (dystonia and tremor).

III. Diagnostic criteria for RTT is based on specific clinical criteria to reflect the main disease features. The clinical presentation associated with typical RTT is defined by a regression of purposeful hand use and spoken language, with the development of gait abnormalities and hand stereotypies. After the period of regression, a stage of stabilization and possibly improvement ensues, with some individuals partially regaining skills. Patients with atypical or variant RTT present with many of the clinical features of typical RTT, such as regression, but do not necessarily have all of the clinical features of typical RTT. There at three known forms of atypical RTT, including but not limited to the preserved speech (Zappella) variant, early onset seizures (Hanefeld) variant, and congenital (Rolando) variant RTT. Additional information about the diagnostic criteria are included in the appendix.

IV. Approximately 90-95% of RTT cases are caused by identifiable mutations of the *MECP2* gene. In 99% of cases, these mutations occur sporadically and are not possessed or transmitted by a child's parents (de novo mutations). Therefore, the vast majority of cases of RTT are not an inherited disorder. Mutations in *MECP2* have also been identified in individuals who do not have the clinical features of RTT, usually a history of regression, and therefore cannot be given a diagnosis of RTT. These clinical phenotypes emphasize that mutations in *MECP2* are not synonymous with RTT and that a mutation in *MECP2* is not sufficient to make the diagnosis of RTT. The diagnosis of RTT is made clinically as *MECP2* mutations are neither necessary nor sufficient to make the diagnosis of RTT.

V. Trofinetide (Daybue) is the first and only treatment FDA-approved to treat RTT. Treatments focus on managing symptoms and preventing complications. In addition to medications to help control specific symptoms, several non-drug approaches may be used to help manage the condition and improve patients' quality of life. All the treatments currently used are solely for management of the numerous complications of the disorder. These treatments include medications for epilepsy, constipation, and other systemic features, therapies to compensate for neurological impairment, and surgical therapies for dysphagia, contracture, and scoliosis are common. Functional abilities can be improved by various interventions such as physiotherapy,

occupational therapy, hydrotherapy, and speech therapy. Given the complexity of the disease, diagnosis by a specialist or provider has consulted with a specialist in the area of the patient's diagnosis, such as a neurologist, pediatrician, or geneticist, is required.

VI. Trofinetide (Daybue) is a synthetic version of a naturally occurring molecule known as glycine-proline-glutamate (GPE), the N-terminal tripeptide of insulin-like growth factor. The mechanism by which trofinetide (Daybue) exerts therapeutic effects in patients with Rett Syndrome (RTT) is unknown. In animal studies, trofinetide has been shown to increase branching of dendrites and synaptic plasticity signals.

VII. The efficacy and safety of trofinetide (Daybue) were evaluated in the Phase 3 LAVENDER study, a 12-week, double-blind, randomized, placebo-controlled study that enrolled 187 female participants 5–20 years of age with RTT. Participants had a diagnosis of typical Rett syndrome according to the Rett Syndrome Diagnostic Criteria with a documented disease-causing mutation in the *MECP2* gene. Participants were randomized to receive trofinetide or matching placebo for 12 weeks. The trofinetide dosage was based on patient weight to achieve similar exposure in all patients. The co-primary endpoints included the Rett Syndrome Behavior Questionnaire (RSBQ) and Clinical Global Impression–Improvement (CGI-I) assessment.

   a. The RSBQ is a 45-item rating scale completed by the caregiver that assesses core symptoms of Rett syndrome (breathing, hand movements or stereotypies, repetitive behaviors, night time behaviors, vocalizations, facial expressions, eye gaze, and mood). Each item is scored as 0 (not true), 1 (somewhat or sometimes true), or 2 (very true or often true), with a maximum possible score of 90 points. Lower scores reflect lesser severity in signs and symptoms of RTT.
      i. The mean baseline RSBQ score was 43.7 for the DAYBUE group and 44.5 for the placebo group.
   b. The CGI-I is rated by clinicians to assess whether a patient has improved or worsened on a 7-point scale (1=very much improved to 7=very much worse) in which a lower score indicates improvement.
      i. Baseline CGI-I score was 4.9 in both groups.

VIII. Trofinetide (Daybue) demonstrated a statistically significant improvement over placebo in both co-primary endpoints. The RSBQ score change in trofinetide (Daybue) group was -4.9 compared to -1.7 change in placebo group was at week 12 (-3.2; 95% CI (-5.7, -0.6), p=0.018). The CGI-I score was 3.5 in the treatment group compared to 3.8 in the placebo group at week 12 (-0.3; 95% CI (-0.5- -0.1); p=0.003). A post-hoc analysis of CGI-I scores was conducted, which revealed that 61% of patients in the trofinetide (Daybue) had no change in RTT symptoms, while 25% had minimal improvement and 13% were much improved. In the placebo group, 81 % of patients had no change, 11% were minimally improved, and 5% were much improved.

IX. The common adverse events were diarrhea (81% with trofinetide vs 19% with placebo) and vomiting (27% with trofinetide vs 10% with placebo). About 12% of trofinetide-treated subjects compared to 4% of placebo-treated subjects experienced weight loss of greater than 7% of body

weight. Although a majority (>95%) of adverse events were rated as mild to moderate, the label warnings and precautions include diarrhea and weight loss to ensure prescribers and patients are aware of these adverse reactions. Treatment was discontinued in 17% individuals in the trofinetide group compared to 2% in the placebo group due to treatment related adverse events, with diarrhea (15%) as the most common adverse reaction leading to discontinuation. Due to the frequency of diarrhea, concomitant therapy with loperamide was initiated in over 50% of subjects in the LAVENDER trial.

X. Although the LAVENDER trial enrolled patients age 5-20 years of age, trofinetide (Daybue) is FDA approved for the treatment of RTT in adults and pediatric patients 2 years of age and older. Efficacy in pediatric patients with RTT aged 2 to 4 years old was provided by an open-label PK study in which 13 patients completed 12 weeks of treatment with trofinetide (Daybue). Exposure and adverse reactions in pediatric patients 2 to 4 years of age treated with trofinetide (Daybue) were similar to those reported in adult and pediatric patients 5 years of age and older in the LAVENDER study.

XI. The inclusion criteria in the LAVENDER study enrolled all female participants, required all participants to have a diagnosis of classic or typical RTT (per diagnostic criteria from Neul et al. 2010), and confirmed *MECP2* mutation. The study excluded patients with atypical RTT, patients without a documented *MECP2* mutation, and male subjects to reduce variability and allow for a more homogeneous study population. Coverage of trofinetide (Daybue) will be considered for individuals with a confirmed clinical diagnosis of typical RTT and presence of *MECP2* mutation to mirror the study population. As of July 2023, efficacy and safety of trofinetide (Daybue) in patients with atypical RTT is unknown.

XII. The available evidence demonstrates statistically significant improvements in the primary endpoints studied, RSBQ and CGI-I, when trofinetide (Daybue) was compared to placebo. There is low to moderate confidence that trofinetide (Daybue) provides clinically meaningful symptom relief or affects physical functioning due to lack of established minimal clinically important differences in the RSBQ and CGI-I scoring instruments. Additionally, the scoring instruments used as primary outcomes are subjective in nature and introduce assessment bias concerns. The impact of trofinetide (Daybue) on morbidity, mortality, or health-related quality of life among patients with RTT is also unknown. The impact of trofinetide (Daybue) on disease activity over time is unknown, however long-term data is currently being assessed in two Phase 3 open-label extension trials (LILAC-1, LILAC-2).

Investigational or Not Medically Necessary Uses

I. Trofinetide (Daybue) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Pediatric patients less than 2 years of age

B. Atypical or variant Rett syndrome (e.g., preserved speech (Zappella) variant, early onset seizures (Hanefeld) variant, and congenital (Rolando) variant)
C. *MECP2*-mutation related disorders without clinical diagnostic symptoms of classic/typical Rett syndrome (e.g., *MECP2*-related severe neonatal encephalopathy, *PPMX*-syndrome, *MECP2* duplication syndrome)
D. Other neurogenerative disorders or disorders that may have symptoms or physical features that are similar to Rett syndrome (e.g., autism spectrum disorder, encephalitis, spastic ataxia, cerebral palsy, spinocerebellar degeneration, leukodystrophies, neuroaxonal dystrophy)
E. *CDKL5*-mutation disorders (e.g., infantile spasms, West syndrome, Lennox-Gastaut syndrome)
F. Other metabolic or degenerative disorders (e.g., neuronal ceroid lipofuscinosis, phenylketonuria, and urea cycle disorders)
G. *FOXG1*-mutation related disorders
H. Pitt-Hopkins syndrome
I. Angelman syndrome

Appendix

I. Table 1: Quantity Limit/Dosing
   A. Available dosage form: Trofinetide 200mg/mL oral solution is available as a 450mL strawberry flavored oral solution in 500mL bottle
   B. Per the label, any unused trofinetide (Daybue) should be discarded after 14 days of first opening the bottle
   C. The dose prescribed is appropriate based on the individual's weight:

Patient Weight	Trofinetide (Daybue) Dosing	Trofinetide (Daybue) Volume	mL/Day supply (DS)	# Bottles/Day supply (DS)
9kg to less than 12kg	5,000 mg twice daily	25mL twice daily	1,500mL/27 days	3 bottles/27 days
12kg to less than 20kg	6,000 mg twice daily	30mL twice daily	2,000mL/30 days	4 bottles/30 days
20kg to less than 35kg	8,000 mg twice daily	40mL twice daily	2,500mL/28 days	5 bottles/28 days
35kg to less than 50kg	10,000 mg twice daily	50mL twice daily	3,000mL/28 days	6 bottles/28 days
50kg or more	12,000 mg twice daily	60mL twice daily	4,000mL/30 days	8 bottles/30 days

II. Table 2. Rett Syndrome Diagnostic Criteria (Source: Neul et al. 2010)

Required for typical or classic RTT
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 for typical RTT
1. Brain injury secondary to trauma (peri- or postnatally), neurometabolic disease, or severe infection that causes neurological problems[***] 2. Grossly abnormal psychomotor development in first 6 months of life[#]
Required for atypical or variant RTT
1. A period of regression followed by recovery or stabilization[*] 2. At least 2 out of the 4 main criteria 3. 5 out of 11 supportive criteria
Supportive Criteria for atypical RTT[##]
1. Breathing disturbances when awake 2. Bruxism when awake 3. Impaired sleep pattern 4. Abnormal muscle tone 5. Peripheral vasomotor disturbances 6. Scoliosis/kyphosis 7. Growth retardation 8. Small cold hands and feet 9. Inappropriate laughing/screaming spells 10. Diminished response to pain 11. Intense eye communication - “eye pointing”
[*]Because *MECP2* mutations are now identified in some individuals prior to any clear evidence of regression, the diagnosis of “possible” RTT should be given to those individuals under 3 years old who have not lost any skills but otherwise have clinical features suggestive of RTT. These individuals should be reassessed every 6–12 months for evidence of regression. If regression manifests, the diagnosis should then be changed to definite RTT. However, if the child does not show any evidence of regression by 5 years, the diagnosis of RTT should be questioned. [**]Loss of acquired language is based on best acquired spoken language skill, not strictly on the acquisition of distinct words or higher language skills. Thus, an individual who had learned to babble but then loses this ability is considered to have a loss of acquired language. [***]There should be clear evidence (neurological or ophthalmological examination and MRI/CT) that the presumed insult directly resulted in neurological dysfunction. [#]Grossly abnormal to the point that normal milestones (acquiring head control, swallowing, developing social smile) are not met. Mild generalized hypotonia or other previously reported subtle developmental alterations during the first six months of life is common in RTT and do not constitute an exclusionary criterion. [##]If an individual has or ever had a clinical feature listed it is counted as a supportive criterion. Many of these features have an age dependency, manifesting and becoming more predominant at certain ages. Therefore, the diagnosis of atypical RTT may be easier for older individuals than for younger. In the case of a younger individual (under 5 years old) who has a period of regression and ≥2 main criteria but does not fulfill the requirement of 5/11 supportive criteria, the diagnosis of “probably atypical RTT” may be given. Individuals who fall into this category should be reassessed as they age and the diagnosis revised accordingly.

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Related Policies

Currently there are no related policies.

Policy Implementation/Update

Action and Summary of Changes	Date
Policy created	08/2023