BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY COVERAGE GUIDELINE

DAYBUE™ (trofinetide) oral
Generic Equivalent (if available)

This Pharmacy Coverage Guideline (PCG):
- Provides information about the reasons, basis, and information sources we use for coverage decisions
- Is not an opinion that a drug (collectively "Service") is clinically appropriate or inappropriate for a patient
- Is not a substitute for a provider's judgment (Provider and patient are responsible for all decisions about appropriateness of care)
- Is subject to all provisions e.g. (benefit coverage, limits, and exclusions) in the member's benefit plan; and
- Is subject to change as new information becomes available.

Scope
- This PCG applies to Commercial and Marketplace plans
- This PCG does not apply to the Federal Employee Program, Medicare Advantage, Medicaid or members of out-of-state Blue Cross and/or Blue Shield Plans

Instructions & Guidance
- To determine whether a member is eligible for the Service, read the entire PCG.
- This PCG is used for FDA approved indications including, but not limited to, a diagnosis and/or treatment with dosing, frequency, and duration.
- Use of a drug outside the FDA approved guidelines, refer to the appropriate Off-Label Use policy.
- The "Criteria" section outlines the factors and information we use to decide if the Service is medically necessary as defined in the Member's benefit plan.
- The "Description" section describes the Service.
- The "Definition" section defines certain words, terms or items within the policy and may include tables and charts.
- The "Resources" section lists the information and materials we considered in developing this PCG
- **We do not accept patient use of samples as evidence of an initial course of treatment, justification for continuation of therapy, or evidence of adequate trial and failure.**
- Information about medications that require prior authorization is available at www.azblue.com/pharmacy. You must fully complete the request form and provide chart notes, lab workup and any other supporting documentation. The prescribing provider must sign the form. Fax the form to BCBSAZ Pharmacy Management at (602) 864-3126 or email it to Pharmacyprecert@azblue.com.

Criteria:

➢ **Criteria for initial therapy:** Daybue (trofinetide) and/or generic equivalent (if available) is considered ***medically necessary*** and will be approved when **ALL** the following criteria are met:

1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with a Pediatric Neurologist

2. Individual is 2 years of age or older weighing at least 9 kg

3. Individual has a confirmed diagnosis of classic/typical Rett syndrome according to the Rett Syndrome Diagnostic Criteria (see Definitions section)

4. **ALL** of the following criteria for classic or typical RTT (see Definitions section)

a. There is a period of regression followed by recovery or stabilization
b. Individual has partial or complete loss of acquired purposeful hand skills
c. Individual has partial or complete loss of acquired spoken language
d. Individual has gait abnormalities: impaired (dyspraxia) or absence of ability
e. Individual has stereotypic hand movements such as hand wringing/squeezing, clapping/tapping, mouthing, and washing/rubbing automatisms

5. Individual completed **ALL** the following **baseline tests** before initiation of treatment and will have continued monitoring as clinically appropriate:
   a. Rett Syndrome Clinical Severity Scale (RSCSS) rating of 10-36
   b. Rett Syndrome Behavior Questionnaire (RSBQ) score
   c. Clinical Global Impression-Severity (CGI-S) score of 4 or more

6. Individual **does not have**: (see Definitions section)
   a. Brain injury secondary to trauma (peri- or postnatally), neurometabolic disease, or severe infection that causes neurological problems
   b. Grossly abnormal psychomotor development in first six months of life

7. **ALL** of the following:
   a. Documented disease-causing pathogenic mutation in *MECP2* gene
   b. Individual is in the post-regression stage of RTT
   c. There has been no loss or degradation in ambulation, hand function, speech, nonverbal communicative or social skills within the last 6-months
   d. If the individual has seizures there is a stable pattern of seizures, or has had no seizures, within the last 2-months

8. **If available:** Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

9. Individual is not currently taking any other drugs which may result in a significant drug interaction that may requiring discontinuation such as OATP1B1 AND OATP1B3 substrates (e.g., methotrexate, cisplatin, atorvastatin, pravastatin, rosuvastatin, bosentan, glyburide, others)

10. Individual does not have severe renal impairment (eGFR less than 30 mL/min for adults or less than 30 mL/min/1.73m^2 for pediatric individuals)

Initial approval duration: 6 months

- **Criteria for continuation of coverage (renewal request):** Daybue (trofinetide) and/or generic equivalent (if available) is considered ***medically necessary*** and will be approved when **ALL** the following criteria are met **(samples are not considered for continuation of therapy)**:

1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with a Pediatric Neurologist

2. Individual has documentation of positive clinical response to therapy defined as the following:

a. Significant improvement (i.e., at least a 3-point change) in Rett Syndrome Behavior Questionnaire (RSBQ) score over baseline **or** score has not worsened
b. Clinical Global Impression-Improvement (CGI-I) score < 4 **or** CGI-Severity score has not worsened

3. Individual has been adherent with the medication

4. **If available:** Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

5. Individual has not developed any contraindications or other significant adverse drug effects that may exclude continued use such as:
   a. Severe diarrhea
   b. Severe dehydration
   c. Significant weight loss
   d. Severe vomiting

6. Individual is not currently taking any other drugs which may result in a significant drug interaction that may requiring discontinuation such as OATP1B1 AND OATP1B3 substrates (e.g., methotrexate, cisplatin, atorvastatin, pravastatin, rosuvastatin, bosentan, glyburide, others)

7. Individual does not have severe renal impairment (eGFR less than 30 mL/min for adults or less than 30 mL/min/1.73m^2 for pediatric individuals)

Renewal duration: 12 months

- Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

  1. **Off-Label Use of Non-Cancer Medications**

  2. **Off-Label Use of Cancer Medications**

Description:

Daybue (trofinetide) is indicated for the treatment of Rett syndrome in adults and pediatric patients 2 years of age and older.

Rett syndrome (RTT) is a neurodevelopmental disorder that occurs almost exclusively in females. Manifestations of typical RTT include a period of regression with loss of purposeful hand skills and spoken language, gait abnormalities, and stereotypic hand movements. Additional features of RTT include growth failure, epilepsy, disorganized breathing pattern, bone mineral deficit and fractures, autonomic nervous system dysfunction, cardiac abnormalities, tone abnormalities and involuntary movements such as dystonia and tremor and sleep

disturbances. Most cases result from mutations in the *MECP2* gene. Mutations in *MECP2* have been detected in approximately 95 percent of classic sporadic RTT cases and 75 percent of atypical RTT cases.

It may be useful to think of RTT as having stages that may be helpful to track the clinical course. However, it is difficult to precisely determine the transitions between stages. Stage I consists of developmental arrest. The onset is between 6-18 months, and it may last for many months. Stage II consists of rapid deterioration or regression. The onset is typically between 1-4 years of age. Stage III begins at 2-10 years of age, following the period of rapid deterioration. This phase lasts many years. Stage IV consists of late motor deterioration and usually begins after the age of 10 years.

Typical RTT patients initially develop normally and then experience loss of speech and purposeful hand use and onset of stereotypic hand movement and gait abnormalities. Additional manifestations can include seizures, autistic features, intermittent breathing abnormalities, autonomic nervous system dysfunction, cardiac abnormalities, and sleep disturbances. Atypical RTT contains variants of RTT that have many but not all of the clinical features of typical RTT. The three defined RTT variants are the preserved speech, early-onset seizure, and congenital variants.

There is no disease modifying therapy for RTT. Specific issues that require consideration include growth failure and nutrition, bone quality, epilepsy, breathing dysfunction, cardiac abnormalities, scoliosis, sleep disturbance, and motor dysfunction. Most deaths were caused by cardiopulmonary factors. Risk factors associated with mortality in classic RTT include ambulation, weight, and seizures.

According to the package label, the efficacy of Daybue (trofinetide) for the treatment of Rett syndrome was established in a 12-week randomized double-blind placebo-controlled study in 187 patients with Rett syndrome who were 5-20 years of age. The diagnosis of typical Rett syndrome was according to the Rett Syndrome Diagnostic Criteria with a documented disease-causing mutation in the *MECP2* gene. Patients were randomized to receive Daybue (trofinetide) (N = 93) or matching placebo (N = 94) for 12 weeks.

The *co-primary efficacy measures* were change from baseline after 12 weeks of treatment in the total score of the Rett Syndrome *Behavior Questionnaire (RSBQ)* and the *Clinical Global Impression-Improvement (CGI-I)* score.

The RSBQ is a 45-item rating scale completed by the caregiver that assesses a range of symptoms of Rett syndrome (general mood, breathing problems, hand movements or stereotypies, face movements, body rocking/expressionless face, repetitive behaviors, night-time behaviors, vocalizations, facial expressions, eye gaze, walking/standing, and fear/anxiety). 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 Rett syndrome.

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, 2 = much improved, 3 = minimally improved, 4 = no change, 5 = minimally worse, 6 = much worse, 7 = very much worse) in which a decrease in score indicates improvement.

Treatment with Daybue (trofinetide) demonstrated a statistically significant difference in favor of Daybue (trofinetide) as compared to placebo on the co-primary efficacy endpoints, the change from baseline in RSBQ total score and the CGI-I score at week 12.

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Definitions:

U.S. Food and Drug Administration (FDA) MedWatch Forms for FDA Safety Reporting
MedWatch Forms for FDA Safety Reporting | FDA

Required criteria 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
Required criteria 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
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 (dyspraxia) or absence of ability 4. Stereotypic hand movements such as hand wringing/squeezing, clapping/tapping, mouthing, and washing/rubbing automatisms
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 (e.g., "eye pointing")
Exclusion criteria for typical RTT
1. Brain injury secondary to trauma (peri- or postnatally), neurometabolic disease, or severe infection that causes neurological problems$^{\Delta}$ 2. Grossly abnormal psychomotor development in first six months of life$^{\lozenge}$

* 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 three years old who have not lost any skills but otherwise have clinical features suggestive of RTT. These individuals should be reassessed every 6 to 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 five 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.

§ 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.

Δ 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 five years old) who has a period of regression and ≥ 2main 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.

◊ There should be clear evidence (neurological or ophthalmological examination and MRI/CT) that the presumed insult directly resulted in neurological dysfunction.

Rett Syndrome Clinical Severity Scale (RTT-CSS or RSCSS)
A thirteen-item clinician measure of severity based on 13 individual, ordinal categories measuring clinical features common in RTT. The CSS form evaluates age at onset of regression (range 1–5), somatic and head growth status (range 0–8), motor (range 0–19), communication (range 0–9), and RTT behaviors/other neurologic symptoms (range 0–17). Scores for all items were summed to create a total score (range 1–58).

Manifestation	Score	Definition
Age of onset of regression	1	>30 months
	2	18 months to 30 months
	3	12 months to <18 months
	4	6 months to <12 months
	5	<6 months
Ambulation	0	Acquired <18 months/Apraxic gait
	1	18 months ≤ 30 months walks alone
	2	>30 months walks alone
	3	>50 months or walks with help
	4	Lost
	5	Never acquired
Autonomic symptoms	0	None
	1	Pink but cool

	2	Mottled and cold
	3	Blue-purple and cold hands or feet
	4	Blue-purple and cold hands and feet
Epilepsy/Seizures	0	Absent
	1	< monthly
	2	< weekly to monthly seizures
	3	Weekly
	4	More than weekly
	5	Infantile spasms
Hand use	0	Acquired & conserved
	1	Holding of objects acquired on time (by 6-8 months) & partially conserved
	2	Holding of objects acquired late (>10 months) and partially conserved
	3	Holding of objects acquired & lost all acquisitions
	4	Never acquired
Head growth	0	None to minimal deceleration (0-1 centile,)
	1	Deceleration>2 centiles, OFC >10th after 24 months
	2	2nd-10th centile after 24 months
	3	2nd-10th centile before 24 months
	4	<2nd centile by 24 months
Language	0	Preserved, contextual
	1	Short phrases only
	2	Single words
	3	Vocalization, babbling
	4	Screaming, no utterances
Motor/Independent sitting	0	Sits alone acquired ≤8mos
	1	Sit with delayed acquisition >8 months
	2	Sit with delayed acquisition >18 months
	3	Sit with delayed acquisition >30 months
	4	Lost
	5	Never acquired
Nonverbal Communication	0	Preserved & propositive (points consistently with finger or eyes)
	1	Good eye contact maintained (≥30 seconds)
	2	Intermittent eye contact (5 seconds to <30 seconds)
	3	Infrequent eye contact (<5 seconds)
	4	Lost and not regained

	5	None
Onset of stereotypies	0	≥10 years
	1	36 months to <10 years
	2	18 to <36 months
	3	12 to <18 months
	4	<12 months
Respiratory dysfunction	0	None
	1	Minimal hyperventilation and/or apnea (<10% of time)
	2	Intermittent hyperventilation and/or apnea (50 % of time)
	3	Constant hyperventilation and/or apnea without cyanosis (100% of time)
	4	Constant hyperventilation or apnea with cyanosis
Scoliosis	0	None
	1	1^0 to $<20^0$
	2	20^0 to $<40^0$
	3	40^0 to $<60^0$
	4	$\geq 60^0$
	5	Surgery
Somatic growth	0	No growth failure
	1	decrease in BMI >1SD (11^{th}-25^{th} %)
	2	decrease in BMI >2SD (5^{th}-10^{th} %)
	3	decrease in BMI >3SD ($<5^{th}$ %)
	4	decrease in BMI >4 SD ($<<5^{th}$ %)

Rett Syndrome Behavior Questionnaire (RSBQ)
A validated caregiver-completed rating scale assessing a wide range of neurobehavioral symptoms known to be impaired in RTT. The RSBQ has been correlated with functioning and quality of life and characterized across a range of ages and genetic variations in RTT. The scale includes 45 items rated on a Likert scale from 0 to 2, 39 of them grouped into *8 subscales* (*1. General Mood, 2. Breathing Problems, 3. Hand Behaviors, 4. Repetitive Face Movements, 5. Body Rocking and Expressionless Face, 6. Night-time Behaviors, 7. Fear/Anxiety, and 8. Walking/Standing*) whose *ratings reflect severity and frequency of symptoms*. A total, representing the sum of the 45 items (maximum score 90), and 8 subscale scores are obtained.

Rett syndrome behavioral questionnaire (RSBQ): Emotional & Disruptive Behavior, Breathing Problems, Hand & Other Stereotypies, Facial Movements, Rocking & Hyporeactivity, Fear/Anxiety		
Score each item as 0 (not true), 1 (somewhat or sometimes true), or 2 (very true or often true)		
General Mood:		
2.	Spells of screaming for no apparent reason during the day	

14.	Abrupt changes in mood	
15.	Certain periods when performs much worse than usual	
16.	Times when miserable for no apparent reason	
22.	Screams hysterically for long periods of time and cannot be consoled	
29.	Times when irritable for no apparent reason	
30.	Spells of inconsolable crying for no apparent reason during the day	
36.	Vocalizes for no apparent reason	
Breathing Problems:		
1.	Times when breathing is deep and fast	
5.	Times when breath is held	
6.	Air or saliva expelled from mouth with force	
19.	Swallows air	
25.	Abdomen fills with air and sometimes feels hard	
Hand Behaviors:		
18.	Does not use hands for purposeful grasping	
20.	Hand movements uniform and monotonous	
21.	Has frequent naps during the day	
24.	Restricted repertoire of hand movement	
35.	Has difficulty in breaking/stopping hand stereotypies	
43.	Amount of time spent looking at an object is longer than time spent manipulating or holding	
Repetitive Face Movements:		
4.	Makes repetitive hand movements involving fingers around the tongue	
28.	Makes mouth grimaces	
32.	Makes repetitive tongue movements	
34.	Makes grimacing expressions with face	
Body Rocking/Expressionless Face:		
12.	Expressionless face	
17.	Seems to look through people into the distance	
31.	Uses eye gaze to convey feelings, needs, and wishes (Reverse Coded)	
33.	Rocks self when hands are prevented from moving	
40.	Tendency to bring hands together in front of chin or chest	
41.	Rocks body repeatedly	
Night—time Behaviors:		
13.	Spells of screaming for no apparent reason during the night	
37.	Spells of laughter for no apparent reason during the night	

42.	Spells of inconsolable crying for no apparent reason during the night	
Fear/Anxiety:		
7.	Spells of apparent anxiety / fear in unfamiliar situations	
9.	Seems frightened when sudden changes in body position	
10.	Times when parts of body held rigid	
38.	Spells of apparent panic	
Walking/Standing:		
23.	Although can stand independently, tends to lean on objects or people	
39.	Walks with stiff legs	
Items not included in subscales:		
3.	Makes repetitive **hand** movements, hands apart	
8.	**Grinds teeth**	
11.	Shift **gaze** with slow horizontal turn of head	
26.	Spells of **laughter** for no apparent reason during the **day**	
27.	Has wounds on **hands** as a result of repetitive hand movements	
44.	Appears **isolated**	
45.	Vacant "**staring**" spells	
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 Rett syndrome. 39 of 45 items grouped into 8 subscales (1. General Mood, 2. Breathing Problems, 3. Hand Behaviors, 4. Repetitive Face Movements, 5. Body Rocking and Expressionless Face, 6. Night-time Behaviors, 7. Fear/Anxiety, and 8. Walking/Standing) whose ratings reflect severity and frequency of symptoms.		

Clinical Global Impression (CGI) scores (CGI-I & CGI-S)
The CGI-I is rated by clinicians to assess whether a patient has improved or worsened on a 7-point scale. A decrease in score indicates improvement. CGI-S is also rated by clinicians used to assess severity of illness. It uses a 7-point scale, lower scores indicate less severity.

Score	Clinical Global Impression – Improvement (CGI-I)	Clinical Global Impression – Severity (CGI-S)
1	Very much improved	Normal
2	Much improved	Borderline ill
3	Minimally improved	Mildly ill
4	No change	Moderately ill
5	Minimally worse	Markedly ill
6	Much worse	Severely ill
7	Very much worse	Extremely ill

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Resources:

Daybue (trofinetide) product information, revised by Acadia Pharmaceuticals Inc. 09-2024. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed June 27, 2025.

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ClinicalTrials.gov Bethesda (MD): National Library of Medicine (US). Identifier NCT04181723: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study of Trofinetide for the Treatment of Girls and Women With Rett Syndrome. Available from: http://clinicaltrials.gov. Last update posted November 02, 2022. Last verified October 2022. Accessed March 30, 2023. Re-evaluated September 24, 2025.

ClinicalTrials.gov Bethesda (MD): National Library of Medicine (US). Identifier NCT02715115: A Randomized, Double-blind, Placebo-controlled, Dose-ranging Study of the Safety and Pharmacokinetics of Oral NNZ-2566 in Pediatric Rett Syndrome. Available from: http://clinicaltrials.gov. Last update posted August 14, 2020. Last verified August 2020. Accessed March 30, 2023. Re-evaluated September 24, 2025.

ClinicalTrials.gov Bethesda (MD): National Library of Medicine (US). Identifier NCT01703533: A Phase II Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Dose-Escalation Study of NNZ-2566 in Rett Syndrome. Available from: http://clinicaltrials.gov. Last update posted February 05, 2018. Last verified January 2018. Accessed September 01, 2023. Re-evaluated September 24, 2025.