trofinetide (Daybue™)

Policy # 00840
Original Effective Date: 07/10/2023
Current Effective Date: 07/10/2023

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider trofinetide (Daybue™)‡ for the treatment of Rett syndrome to be **eligible for coverage.****

Patient Selection Criteria

Coverage eligibility for the use of trofinetide (Daybue) will be considered when all of the following criteria are met:

- Initial:
  - Patient has a diagnosis of Rett syndrome confirmed by ALL of the following:
    - Patient has partial or complete loss of acquired purposeful hand skills; AND
    - Patient has partial or complete loss of acquired spoken language; AND
    - Patient has gait abnormalities (impaired gait or absence of ability); AND
    - Patient has stereotypic hand movements such as hand wringing/squeezing, clapping/tapping, mouthing, or washing/rubbing automatisms; AND
    - Patient does NOT have a history of brain injury secondary to trauma, neurometabolic disease, or severe infection; AND
    - Patient did NOT have grossly abnormal psychomotor development in the first 6 months of life; AND
  - Patient is greater than or equal to 2 years of age; AND
  - Patient has a mutation in the *MECP2* gene; AND
    *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*
  - Patient has an RTT Clinical Severity scale rating between 10-36; AND

*(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*

- Patient has a Clinical Global Impression-Severity score greater than or equal to 4.
  *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*

- Continuation
  - Patient has received an initial authorization; AND
  - According to the provider, patient has experienced improvement in disease symptoms while on therapy.
    *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*

When Services Are Considered Not Medically Necessary

Based on review of available data, the Company considers the use of trofinetide (Daybue) for patients without a mutation in the *MECP2* gene, or who do not have an RTT Clinical Severity Scale rating between 10-36, or with a Clinical Global Impression-Severity Score greater than or equal to 4 to be **not medically necessary.****

Based on review of available data, the Company considers the continued use of trofinetide (Daybue) when the patient has not experienced improvement in disease symptoms while on therapy to be **not medically necessary.****

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of trofinetide (Daybue) when patient selection criteria are not met (except those denoted above as **not medically necessary****) to be **investigational.***

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Background/Overview

Daybue is an oral solution indicated for the treatment of Rett syndrome in adults and pediatric patients 2 years of age and older. It is administered by mouth or via G tube twice daily and is thought to work by enhancing neuronal synaptic function and morphology. One of the major side effects of the treatment is diarrhea, which led to treatment discontinuation of 15% of the patients in the pivotal trial. It is possible that this may be able to be managed with antidiarrheals and discontinuation of laxatives since many patients are on chronic laxative therapy for disease induced constipation.

Rett syndrome (RTT) is a rare genetic (X-linked) neurodevelopmental disorder that occurs almost exclusively in females. The condition is caused by mutations on the X chromosome on the *MECP2* gene. RTT affects approximately 1 in 10,000 to 15,000 live female births. It is a spectrum disorder, with patients exhibiting a broad range of severity. Children with RTT typically seem to experience normal growth and development up to 18 months of age, followed by a period of clinical regression between 1 and 4 years of age. The most pronounced changes are characterized by central nervous system (CNS) impairment, including complete or partial loss of expressive language and purposeful hand use, gait abnormalities, and stereotypic hand movements such as hand wringing/squeezing, and clapping/tapping or rubbing. People living with RTT may also experience additional symptoms that can vary greatly in severity from person to person, such as unusual eye movements, seizures, breathing problems, gastrointestinal complications, skeletal abnormalities, neuroendocrine abnormalities, disruptive and anxiety-like behaviors, as well as mood dysregulation and sleep disturbances.

Before the approval of Daybue, there were no FDA-approved treatments for RTT. Nonpharmacologic treatment focuses primarily on management of symptoms. Medications may be used to improve breathing or motor function, and anticonvulsants may be used to control seizures. Supportive care may include occupational and physical therapy as well as academic, social, vocational, and other services.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Daybue is approved for the treatment of Rett syndrome in adults and pediatric patients 2 years of age and older.

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Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

The efficacy of Daybue for the treatment of Rett syndrome was established in a 12-week randomized, double-blind, placebo-controlled study in patients with Rett syndrome 5 to 20 years of age. Patients (n=187) had a diagnosis of typical Rett syndrome according to the Rett Syndrome Diagnostic Criteria with a documented disease-causing mutation in the *MECP2* gene. Patients were randomized to receive Daybue (n=93) or matching placebo (n=94) for 12 weeks. The Daybue dosage was based on patient weight to achieve similar exposure in all patients.

The coprimary efficacy measures were change from baseline after 12 weeks of treatment in the total score of the Rett Syndrome Behaviour 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 (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 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 to 7=very much worse) in which a decrease in score indicates improvement. Treatment with Daybue demonstrated a statistically significant difference in favor of Daybue as compared to placebo in both primary endpoints. The least-squares mean difference in the RSBQ from baseline to Week 12 was -4.9 in the Daybue group and -1.7 in the placebo group (p=0.018). The mean CGI-I score at week 12 was 3.5 in the Daybue group and 3.8 in the placebo group (p=0.003).

References

1. Daybue [package insert]. Acadia Pharmaceuticals, Inc. San Diego, CA. Updated March 2023.
2. Daybue (trofinetide) New Drug Review. IPD Analytics. Updated March 2023.

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Policy History

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06/01/2023 Medical Policy Committee review
06/14/2023 Medical Policy Implementation Committee approval. New policy.
Next Scheduled Review Date: 06/2024

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and

C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.