Oscar Clinical Guideline: Daybue (trofinetide) (PG148, Ver. 1)

Daybue (trofinetide)

Disclaimer

Clinical guidelines are developed and adopted to establish evidence-based clinical criteria for utilization management decisions. Clinical guidelines are applicable according to policy and plan type. The Plan may delegate utilization management decisions of certain services to third parties who may develop and adopt their own clinical criteria.

Coverage of services is subject to the terms, conditions, and limitations of a member's policy, as well as applicable state and federal law. Clinical guidelines are also subject to in-force criteria such as the Centers for Medicare & Medicaid Services (CMS) national coverage determination (NCD) or local coverage determination (LCD) for Medicare Advantage plans. Please refer to the member's policy documents (e.g., Certificate/Evidence of Coverage, Schedule of Benefits, Plan Formulary) or contact the Plan to confirm coverage.

Summary

Rett syndrome (OMIM 312750), a rare neurodevelopmental disorder primarily affecting females, has an incidence of approximately 1 in 15,000 live births. Males with Rett syndrome frequently experience severe encephalopathy with a metabolic-degenerative pattern that often begins shortly after birth, and death frequently occurs before the age of two years.

- The diagnosis of a MECP2 disorder, which includes Rett syndrome, is typically established through molecular genetic testing. In a female proband, this diagnosis would require suggestive findings and a heterozygous pathogenic variant in the MECP2 gene. Similarly, in a male proband, suggestive findings and a hemizygous MECP2 pathogenic variant are necessary for diagnosis.
- MECP2 disorders exhibit X-linked inheritance, with more than 99% of cases arising due to a de novo pathogenic variant. The severity of the syndrome can vary significantly, often influenced by factors such as gender and X-inactivation in females. While genotype-phenotype correlations exist, they are not consistently observed across all cases.

Normal development in infants with Rett syndrome usually continues until about 6 to 18 months of age, followed by a period of regression where previously acquired skills are lost. Symptoms manifest as loss of purposeful hand skills, impaired language, and motor control, diminished social engagement, repetitive movements, and potential complications such as muscle weakness, joint contractures, scoliosis, and seizures. The syndrome also impacts life expectancy, typically in females reducing it to around 40 to 50 years.

Historically, no FDA-approved therapies have specifically targeted the root cause of Rett syndrome. The mainstay of management has been symptomatic treatment, focusing on managing the wide range of manifestations and complications associated with the disorder. Supportive therapies are tailored to address specific symptoms such as epilepsy, constipation, dysphagia, contractures, and scoliosis, aiming to improve the quality of life and alleviate symptom severity, but these interventions do not provide a cure.

Daybue (trofinetide) is indicated for the treatment of Rett syndrome in adults and pediatric patients 2 years of age and older. Trofinetide is a synthetic analogue of glypromate, a fragment of insulin-like growth factor-1 (IGF-1), which plays a key role in the development and function of nerve tissue. The drug is administered orally or via G-tube twice a day, with dosage dependent on the patient's weight.

Definitions

"**Clinical Global Impression-Improvement (CGI-I) score**" is a rating scale used to assess the overall improvement or change in a patient's condition following a specific treatment or intervention. It provides a clinician's judgment regarding the extent of improvement observed in the patient's symptoms and functioning.

"**Contractures**" are abnormal and fixed tightening or shortening of muscles, tendons, or other tissues that restrict joint movement. Joint contractures can develop in individuals with Rett syndrome due to muscle weakness and spasticity.

"**Epilepsy**" is a neurological disorder characterized by recurrent seizures, which may occur in individuals with Rett syndrome as a secondary symptom.

"**methyl-CpG binding protein 2 (MECP2) gene**" is located on the X-chromosome, responsible for producing a protein that plays a critical role in brain development and function. Mutations in the MECP2 gene are the primary cause of Rett syndrome.

"**Online Mendelian Inheritance in Man (OMIM)**" is a comprehensive, authoritative, and regularly updated compendium of human genes and genetic disorders.

- Each entry in OMIM has a unique six-digit number that classifies different genetic disorders or gene variations.
- The database is freely available and widely used by researchers and healthcare professionals interested in genetic disorders.
- Each entry in OMIM represents a specific genetic disorder or a gene and has a unique six-digit number. The database provides detailed information about the clinical features, genetics, and molecular biology of the disorder or gene. It serves as a critical resource for clinicians, geneticists, and researchers who are investigating human genetic disorders and the genes that cause them.

The reference to "Rett syndrome-congenital variant (OMIM 613454)" indicates a distinct genetic disorder documented in the OMIM database. It is caused by pathogenic variants in the FOXG1 gene.

"**Quality of Life**" refers to an individual's overall well-being and satisfaction with their physical, mental, and social functioning. In the context of Rett syndrome, improving quality of life involves managing symptoms, optimizing functioning, and enhancing the individual's overall sense of happiness and fulfillment.

"**Regression**" refers to the loss of previously acquired developmental skills, such as language, motor control, and social interaction, that occurs in individuals with Rett syndrome during the period of regression.

"**Rett Syndrome Behaviour Questionnaire (RSBQ)**" is a standardized questionnaire used to assess and measure the behavioral symptoms associated with Rett syndrome. It provides insights into various aspects of the syndrome's behavioral manifestations, such as social engagement, repetitive behaviors, and communication abilities.

"**Scoliosis**" is a sideways curvature of the spine that can occur in individuals with Rett syndrome as a result of muscle weakness and impaired control of posture and movement.

"**Stereotypies**" are repetitive and purposeless movements or behaviors often seen in individuals with Rett syndrome, such as hand-wringing, hand-mouthing, or body rocking.

"**X-Inactivation**" is a process that occurs in females where one of the two X-chromosomes is randomly inactivated in each cell to achieve dosage compensation. X-inactivation can affect the severity and manifestation of Rett syndrome symptoms due to the random inactivation of the X-chromosome carrying the mutated MECP2 gene.

Medical Necessity Criteria for Initial Authorization

The Plan considers **Daybue (trofinetide)** medically necessary when **ALL** of the following criteria are met:

1. The medication is prescribed by or in consultation with a physician who specializes in the treatment of Rett syndrome (e.g., neurology, psychiatry, or genetics); ***AND***
2. The member is 2 years of age or older; ***AND***
3. The member has a diagnosis of Rett Syndrome, with a documented disease-causing mutation in the MECP2 gene by molecular genetic testing. Specifically:
    a. Female probands must have a heterozygous MECP2 pathogenic variant.
    b. Male probands must have a hemizygous MECP2 pathogenic variant.

If the above prior authorization criteria are met, the requested medication will be approved for an initial approval duration of 12 weeks (3 months).

Medical Necessity Criteria for Reauthorization

Reauthorization for 6 months will be granted if the member has recent (within the last 3 months) clinical chart documentation demonstrating **ALL** of the following criteria:

1. The requested medication continues to be prescribed by or in consultation with a physician who specializes in the treatment of Rett syndrome (e.g., neurology, psychiatry, or genetics); ***AND***
2. The member has shown a positive response to the treatment, as indicated by a significant reduction in Rett syndrome symptoms. This response should be evidenced by clinical documentation such as the Rett Syndrome Behaviour Questionnaire (RSBQ) score and/or the Clinical Global Impression-Improvement (CGI-I) score; ***AND***
3. The member has not developed any severe side effects or contraindications directly related to Daybue (trofinetide) use, such as severe diarrhea, dehydration, or significant weight loss, which have led to a requirement of discontinuation of the medication; ***AND***

4. The member continues to be compliant with the medication regimen, and the benefits of continuing Daybue therapy are judged to outweigh any potential risks.

Experimental or Investigational / Not Medically Necessary

Daybue (trofinetide) for any other indication or use is considered not medically necessary by the Plan, as it is deemed to be experimental, investigational, or unproven. Non-covered indications include conditions such as Angelman syndrome, CDKL5 encephalopathy, Rett syndrome congenital variant, or any other condition apart from Rett syndrome. This conclusion is based on the fact that clinical trials for Daybue have specifically studied its safety and effectiveness in individuals with Rett syndrome, not these other conditions. Without rigorous scientific evidence from well-conducted clinical trials, it is not appropriate or safe to use Daybue for conditions other than Rett syndrome. Thus, Daybue is not covered for these non-approved indications.

1. Angelman Syndrome (OMIM 105830) is a complex genetic disorder that primarily affects the nervous system. Characteristic features of this condition include delayed development, intellectual disability, severe speech impairment, and problems with movement and balance (ataxia). It is caused by a loss of function in the UBE3A gene on the maternal 15th chromosome.
2. CDKL5 Encephalopathy (OMIM 300672), also known as CDKL5 deficiency disorder, is a severe neurodevelopmental disorder characterized by early-onset, difficult-to-control seizures, and severe neurodevelopmental delay affecting cognitive, motor, speech, and visual function. The condition is caused by mutations in the CDKL5 gene.
3. Rett Syndrome Congenital Variant (OMIM 613454), is a variant of Rett syndrome caused by pathogenic variants in the FOXG1 gene. While this condition presents with symptoms similar to those of Rett syndrome, it has distinct features and a different genetic basis.
    a. Rett syndrome is a rare genetic neurological disorder that primarily affects girls and leads to severe cognitive and physical impairments. Typically, it is caused by pathogenic variants in the MECP2 gene. However, the "Rett-like" presentations can be seen in disorders that share some of the same symptoms but are caused by mutations in different genes, such as the FOXG1 gene. These cases are sometimes referred to as Rett syndrome-congenital variant.
    b. Thus, it is important for healthcare providers to confirm a Rett syndrome diagnosis through genetic testing, specifically identifying a pathogenic variant in the MECP2 gene. This approach helps distinguish classic Rett syndrome from similar or overlapping disorders, including the Rett syndrome-congenital variant caused by pathogenic variants in the FOXG1 gene (OMIM 613454).

ICD-10-CM (diagnosis) Codes for Rett syndrome

Code	*Description*
F84.2	Rett's syndrome
Q99.8	Other specified chromosome abnormalities

Appendix

Clinical Studies

The effectiveness of DAYBUE, a treatment for Rett syndrome, was demonstrated in a 12-week randomized, double-blind, placebo-controlled study in patients aged 5 to 20 years (Study 1; NCT04181723). The 187 participants had a diagnosis of typical Rett syndrome with a confirmed mutation in the MECP2 gene, known to cause the disease. They were randomized to receive either DAYBUE (N=93) or a matching placebo (N=94) for 12 weeks, with the dosage based on patient weight.

The co-primary efficacy measures were the change from baseline after 12 weeks in the total score of the Rett Syndrome Behaviour Questionnaire (RSBQ) and the Clinical Global Impression-Improvement (CGI-I) score. The RSBQ is a caregiver-completed rating scale assessing various symptoms of Rett syndrome, and lower scores reflect less severity. The CGI-I is rated by clinicians to assess patient improvement or worsening on a 7-point scale, with a decrease in score indicating improvement.

- Treatment with DAYBUE showed a statistically significant difference compared to placebo in the change from baseline in RSBQ total score and the CGI-I score at week 12.
- Specifically, DAYBUE's RSBQ score improved by an average of 4.9 points, 3.2 points more than the placebo group's average improvement of 1.7 points (p-value 0.018). For the CGI-I score, the DAYBUE group improved more than the placebo group with a -0.3 point change (p-value 0.003).

References

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Clinical Guideline Revision / History Information

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