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Risdiplam

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Overview

This policy supports medical necessity review for risdiplam oral solution (Evrysdi®).

Receipt of sample product does not satisfy any criteria requirements for coverage.

Medical Necessity

Risdiplam (Evrysdi) is considered medically necessary when the following are met:

- 1. Spinal Muscular Atrophy. Individual meets ALL of the following criteria (A, B, C, D, E, F, G, and H):
A. Documentation of genetic test confirming the diagnosis of spinal muscular atrophy with bi-allelic mutations in the survival motor neuron 1 (SMN1) gene reported as at least ONE of the following: homozygous deletion, homozygous mutation, or compound heterozygous mutation
B. Individual meets ONE of the following (i or ii):
i. Documentation that individual has two or three survival motor neuron 2 (SMN2) gene copies
ii. Individual meets BOTH of the following (a and b):
a. Individual has four survival motor neuron 2 (SMN2) gene copies

- b. According to the prescriber, the individual has objective signs consistent with spinal muscular atrophy Types 1, 2, or 3
- C. Baseline motor ability assessment that suggests spinal muscular atrophy (based on age, motor ability, and development) is provided from **ONE** of the following exams (i, ii, iii, iv, v, vi, vii, or viii):
 - i. Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III) [Item 22]
 - ii. Children’s Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND)
 - iii. Hammersmith Functional Motor Scale Expanded (HFMSE)
 - iv. Hammersmith Infant Neurological Exam Part 2 (HINE-2)
 - v. Motor Function Measure-32 Items (MFM-32)
 - vi. Revised Upper Limb Module (RULM) Test
 - vii. 6-Minute Walk Test (6MWT)
 - viii. World Health Organization motor milestone scale
- D. For individuals previously treated with Zolgensma, **BOTH** of the following criteria are met (i and ii):
 - i. At least 60 days have passed since Zolgensma administration
 - ii. There has been a documented clinical decline of minimally important clinical difference from pre-treatment baseline or highest post-treatment score achieved on **ONE** of the following motor exams (a,b, c, or d):
 - a. CHOP INTEND: Decline of at least 4 points
 - b. HFMSE: Decline of at least 3 points
 - c. HINE-2: Decline of at least 1 point
 - d. RULM: Decline of at least 2 points
- E. If individual is of childbearing potential, individual is not currently pregnant and has been counseled to use effective contraception during treatment and up until 1 month after the last Evrysdi dose
- F. The individual does not have evidence of hepatic impairment
- G. Dosing of Evrysdi meets **ONE** of the following based on the current kg weight, measured within the past 1 month (i, ii, iii or iv):
 - i. 0.15 mg/kg once daily if the individual is less than 2 months of age
 - ii. 0.2 mg/kg once daily if the individual is 2 months to less than 2 years of age
 - iii. 0.25 mg/kg once daily for individuals 2 years of age or older who weigh less than 20 kg
 - iv. 5 mg once daily for individuals 2 years of age or older who weigh 20 kg or greater
- H. Medication is prescribed by, or in consultation with, a physician who specializes in the management of individuals with spinal muscular atrophy and/or neuromuscular disorders

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

Reauthorization Criteria

Risdiplam (Evrysdi) is considered medically necessary for continued use when initial criteria are met **AND** documentation of beneficial response, including the following:

1. Improvement or stabilization from pretreatment baseline status as evidenced by **ONE** of the following exams, or prescriber monitoring/assessment tools (based on age and motor ability) in the last 4 months:
 - A. Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III) [Item 22]
 - B. Children’s Hospital of Philadelphia Test of Neuromuscular Disorders (CHOP-INTEND)
 - C. Hammersmith Functional Motor Scale Expanded (HFMSE)
 - D. Hammersmith Infant Neurologic Exam Part 2 (HINE-2)
 - E. Motor Function Measure-32 Items (MFM-32)
 - F. Revised Upper Limb Module (RULM) Test
 - G. 6-Minute Walk Test (6MWT)
 - H. World Health Organization motor milestone scale
 - I. Physician monitoring tools (pulmonary function test, bulbar function, and/or reduced need for respiratory support)

Authorization Duration

Initial approval duration is up to 6 months.
Reauthorization approval duration is up to 6 months.

Conditions Not Covered

Any other use is considered experimental, investigational or unproven including the following (this list may not be all inclusive):

- 1. Individual has Complete Paralysis of All Limbs.** Data are needed to determine if this patient population with advanced spinal muscular atrophy would derive benefits from Evrysdi.
- 2. Individual has Permanent Ventilator Dependence.** Data are needed to determine if this patient population with advanced spinal muscular atrophy would derive benefits from Evrysdi.
- 3. Concurrent use of nusinersen (Spinraza)**

Background

OVERVIEW

Evrysdi, a survival motor neuron (SMN)2 splicing modifier, is indicated for the treatment of spinal muscular atrophy in pediatric patients and adults.¹ The recommended dosing is as follows:

- 0.15 mg/kg once daily (QD) for patients < 2 months of age.
- 0.2 mg/kg QD for patients 2 months to < 2 years of age.
- 0.25 mg/kg QD for patients ≥ 2 years of age and < 20 kg.
- 5 mg QD for patients ≥ 2 years of age and ≥ 20 kg.

Disease Overview

Spinal muscular atrophy is a genetic, autosomal recessive muscular disorder caused by deletion or loss of function mutation in the SMN1 gene.²⁻⁵ The reduced level of SMN protein causes degeneration of lower motor neurons.⁵ The phenotypic expression of the disease is impacted by the SMN2 gene copy number. Data have shown that patients with a higher number of SMN2 copies generally have a more mild phenotypic disease expression. Gene deletion testing for spinal muscular atrophy can be performed at many diagnostic laboratories. Table 1 describes the disease types. Of note, various motor ability assessments are used in clinical practice to characterize functional impairment in spinal muscular atrophy. Different functional motor scales are utilized to evaluate patients.⁶ When motor neuron function is lost, it cannot be regained, which greatly impacts patients who have experienced progression (e.g., patients with complete paralysis of limbs or permanent ventilator dependence).¹⁻⁶

Table 1. Types of Spinal Muscular Atrophy.²⁻⁵

| SMA Type | Age at Onset | Features/Clinical Presentation | Lifespan | SMN2 Gene Copy Number |
|----------|------------------|---|--|-----------------------|
| 0 | Prenatal | Severe hypotonia and weakness; respiratory failure at birth. There is no achievement of motor milestones. | A few weeks to < 6 months | 0 to 1 |
| 1 | < 6 months | Poor muscle tone, lack of movement, and respiratory assistance needed at birth. Patients are never able to sit. | < 2 years | 1 to 2 |
| 2 | Before 18 months | Patients are able to sit. However, patients are unable to walk or stand without assistance. | 75% of patients are alive at 25 years of age | 2 to 3 |

| SMA Type | Age at Onset | Features/Clinical Presentation | Lifespan | SMN2 Gene Copy Number |
|----------|--------------|---|----------|-----------------------|
| 3 | > 18 months | Walk independently but may lose this ability as the disease progresses. | Normal | 3 to 4 |
| 4 | Adulthood | Walk until adulthood. | Normal | ≥ 4 |

SMA – Spinal muscular atrophy; SMN2 – Survival motor neuron 2.

In addition to Evrysdi, other therapies are available. **Spinraza**[®] (nusinersen intrathecal injection), a SMN2-directed antisense oligonucleotide, is indicated for the treatment of spinal muscular atrophy in pediatric patients and adults.⁷ Although studies and experience continue, the primary pivotal data include infantile-onset (Type 1) and later-onset (Type 2 and Type 3) spinal muscular atrophy primarily in children. Data are also available with Spinraza in presymptomatic infants who were genetically diagnosed with spinal muscular atrophy. There are some data with Spinraza in adults as well.

Zolgensma[®] (onasemnogene abeparvovec-xioi intravenous infusion), an adeno-associated virus vector-based gene therapy, is indicated for the treatment of pediatric patients < 2 years of age with spinal muscular atrophy with bi-allelic mutations in the SMN1 gene.⁷ The agent works by providing a copy of the gene encoding the SMN protein, which increases its production. Zolgensma is administered as a single-dose intravenous infusion over 60 minutes. Pivotal studies mainly involved infants with two or three SMN2 gene copies with primarily Type 1 or Type 2 disease.

Clinical Efficacy

The efficacy of Evrysdi for the treatment of patients with infantile-onset (Type 1), later-onset (Type 2 and 3), and pre-symptomatic spinal muscular atrophy was evaluated in three clinical studies.^{1,9-11} **FIREFISH** involved patients with Type 1 spinal muscular atrophy who had symptom onset between 28 days and 3 months of age.¹ Genetic confirmation of homozygous deletion or compound heterozygosity predictive of loss of function of the SMN1 gene was required for trial entry. Patients had two SMN2 gene copies. Many patients gained improvements in the ability to sit for at least 5 seconds independently, and there was an increase in the percentages of patients who were alive without permanent ventilation. **SUNFISH** evaluated Evrysdi in patients with later-onset (Type 2 or Type 3) spinal muscular atrophy. Most patients (90%) had three SMN2 gene copies; 8% and 2% of patients had four and two SMN2 gene copies, respectively. In Part 2 of the study, benefits of Evrysdi vs. placebo were noted at Month 12 in motor function as well as in upper limb motor performance. **RAINBOWFISH** investigated Evrysdi in infants up to 6 weeks of age (at the first dose) who had been genetically diagnosed with spinal muscular atrophy but did not have symptoms. In total, seven patients have received Evrysdi for at least 12 months. Four patients had two SMN2 copies, two patients had three SMN2 gene copies, and one patient had four or more SMN2 copies. The median age at first dose among the seven patients was 35 days. The six patients with two or three SMN2 gene copies achieved various motor milestones at Month 12, including the ability to sit. Of note, in general, the onset of effect with Evrysdi was observed after approximately 4 months of therapy. Evrysdi has not been evaluated in patients with fewer than two or more than four SMN2 gene copies.^{1,9-11}

Guidelines

Evrysdi is not addressed in guidelines. According to a treatment algorithm from the Spinal Muscular Atrophy Newborn Screening Multidisciplinary Working Group (2018), immediate treatment is recommended in patients with two or three SMN2 gene copies.¹² In 2020, the Working Group updated recommendations that infants diagnosed with spinal muscular atrophy via newborn screening with four SMN2 gene copies should receive immediate treatment.¹³ Patients with five (or more) SMN2 gene copies should be observed and screened for symptoms.

Safety

Based on animal data, Evrysdi may cause fetal harm if given to a pregnant woman.¹ Pregnancy testing is recommended for females of reproductive potential prior to initiating Evrysdi. Advise females of reproductive potential to use effective contraception during treatment with Evrysdi and for at least 1 month after the last dose.

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