Drug and Biologic Coverage Policy

Risdiplam

Table of Contents

Overview .............................................................. 1
Coverage Policy ................................................... 1
Reauthorization Criteria ....................................... 2
Authorization Duration ......................................... 2
Conditions Not Covered ....................................... 2
Background .......................................................... 3
References .......................................................... 5

Related Coverage Resources

Nusinersen
Onasemnogene Abeparvovec-xioi, Zolgensma

INSTRUCTIONS FOR USE

The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer’s particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer’s benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer’s benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Overview

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

Coverage Policy

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

1. **Individual has Spinal Muscular Atrophy** and ALL of the following:
   a. Individual is ≥ 2 months to ≤ 25 years of age
   b. 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
   c. Individual meets BOTH of the following:
      - Documentation that individual has two to four survival motor neuron 2 (SMN2) gene copies
      - Documentation that individual has objective signs, according to the health care professional, consistent with spinal muscular atrophy Types 1, 2, or 3
d. For individuals who have received prior treatment with Spinraza® (nusinersen injection for intrathecal use), the health care professional attests that further therapy with Spinraza® will be discontinued

e. Individual has NOT received Zolgensma® (onasemnogene abeparvovec-xioi suspension for intravenous infusion) in the past

f. Attestation the individual is not currently pregnant and has been counseled to use effective contraception during treatment and until 1 month after the last Evrysdi dose

g. The individual does not have evidence of hepatic impairment

h. Dosing of Evrysdi meets ONE of the following based on the current (within the past 1 month) kg weight:
   - 0.2 mg/kg once daily if the individual is 2 months to < 2 years of age
   - 0.25 mg/kg once daily for individuals ≥ 2 years of age who weigh < 20 kg
   - 5 mg once daily for individuals ≥ 2 years of age who weigh ≥ 20 kg

i. 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.

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

**Documentation:** When documentation is required, the prescriber must provide written documentation supporting the trials of these other agents. Documentation may include, but is not limited to, chart notes, prescription claims records, and/or prescription receipts.

**Reauthorization Criteria**

Risdiplam (Evrysdi®) is considered medically necessary for continued use when initial criteria are met AND documentation of beneficial response (for example, by an objective measurement and/or assessment tool).

*Note:* Examples of improvement, achievement, and/or maintenance in motor milestones should be demonstrated and can be evaluated by tests such as the Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III) [Item 22], Motor Function Measure-32 Items (MFM-32), Hammersmith Infant Neurologic Exam (HINE) [section 2], Hammersmith Functional Motor Scale Expanded (HFMSE), Children’s Hospital of Philadelphia Test of Neuromuscular Disorders (CHOP-INTEND), as well as other physician monitoring tools [pulmonary function tests showing improvement, bulbar function results, reduced need for respiratory support, and/or prevention of permanent assisted ventilation].

**Authorization Duration**

Initial approval duration is up to 4 months.

Reauthorization approval duration is up to 4 months.

**Conditions Not Covered**

Risdiplam (Evrysdi®) is considered experimental, investigational or unproven for ANY other use including the following (this list may not be all inclusive):

1. **Individual has Complete Paralysis of All Limbs**

2. **Individual has Permanent Ventilator Dependence**
OVERVIEW
Evrysdi, a survival motor neuron 2 (SMN2) splicing modifier, is indicated for the treatment of:¹
- Spinal muscular atrophy in patients 2 months of age and older

The recommended dosing is as follows:
- 0.2 mg/kg once daily (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 for patients ≥ 2 years of age and ≥ 20 kg

Evrysdi For Oral Solution: 60 mg of risdiplam as a powder for constitution to provide 0.75 mg/mL solution.

Disease Overview
Spinal muscular atrophy is a genetic, autosomal recessive muscular disorder caused by deletion or loss of function mutation in the survival motor neuron 1 (SMN1) gene.²⁻⁵ The reduced levels of survival motor neuron (SMN) protein causes degeneration of lower motor neurons.⁵ Although the condition is a multisystem disorder, it is clinically characterized by progressive muscle weakness and atrophy. Among all ethnicities in the US, spinal muscular atrophy affects approximately one in 11,000 infants and has an average carrier frequency of one in 54 individuals; as many as 10,000 to 25,000 children and adults in the US may be impacted.⁶ Although the condition can be present in individuals of any age, it is more frequently diagnosed in infants and children, as it is more severe in this population.²⁻⁵ Proximal muscles (e.g., torso, legs, neck) are more impacted compared with distal muscles (e.g., hands, arms, feet). Without treatment, patients with spinal muscular atrophy may never be able to, or progressively, lose the ability to walk, stand, sit and/or ambulate. More severe disease manifests with poor head control (hypotonia), reduced reflexes, tongue movements and difficulties in swallowing and feeding. Respiratory illnesses and bone and/or spinal deformities may occur. However, cognitive development is not impacted. The phenotypic expression of the disease is impacted by the presence of the SMN2 gene copy number. SMN1 is responsible for producing most of the effective SMN protein, although some SMN protein can be made by the SMN2 gene. Therefore, patients with a deletion of the SMN1 gene may have the potential for making some SMN protein through the SMN2 gene copy, although in most cases the resulting protein made by this gene is truncated and is not as effective or functional. Data have shown that patients with a higher number of SMN2 copies generally have a more mild phenotypic disease expression. Diagnostic testing for spinal muscular atrophy can be performed at many laboratories. Table 1 describes disease types. Type 1 is the most common, followed by Types 2 and 3.

Besides Evrysdi, other therapies are available. Spinraza® (nusinersen injection for intrathecal use), a SMN2-directed antisense oligonucleotide, is indicated for the treatment of spinal muscular atrophy in pediatric and adult patients.⁶ Spinraza is given by intrathecal injection. 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. Trials are evolving with Spinraza in adults. Data are also available in presymptomatic infants who were genetically diagnosed with spinal muscular atrophy.

Zolgensma® (onasemnogene abeparvovec-xioi suspension for 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 survival motor neuron 1 (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 involve infants with two or three SMN2 gene copies with primarily Type 1 or Type 2 disease.

Table 1. Types of Spinal Muscular Atrophy²⁻⁵

<table>
<thead>
<tr>
<th>SMA Type</th>
<th>Age at Onset</th>
<th>Features/Clinical Presentation</th>
<th>Lifespan</th>
<th>SMN2 Copy Gene Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Prenatal</td>
<td>Severe hypotonia and weakness, and respiratory failure at birth. There is no achievement of motor milestones.</td>
<td>A few weeks to &lt; 6 months</td>
<td>0 to 1</td>
</tr>
<tr>
<td>SMA Type</td>
<td>Age at Onset</td>
<td>Features/Clinical Presentation</td>
<td>Lifespan</td>
<td>SMN2 Copy Gene Number</td>
</tr>
<tr>
<td>----------</td>
<td>--------------</td>
<td>---------------------------------</td>
<td>----------</td>
<td>-----------------------</td>
</tr>
<tr>
<td>1</td>
<td>&lt; 6 months</td>
<td>Poor muscle tone, lack of movement, respiratory assistance needed at birth. Patients are never able to sit.</td>
<td>&lt; 2 years</td>
<td>1 to 2</td>
</tr>
<tr>
<td>2</td>
<td>&lt; 18 months</td>
<td>Patients are able to sit. However, patients are unable to walk or stand without assistance.</td>
<td>75% of patients are alive at 25 years of age</td>
<td>2 to 3</td>
</tr>
<tr>
<td>3</td>
<td>&gt; 18 months</td>
<td>Walks independently but may lose this ability as the disease progresses.</td>
<td>Normal</td>
<td>3 to 4</td>
</tr>
<tr>
<td>4</td>
<td>Adulthood</td>
<td>Walk until adulthood.</td>
<td>Normal lifespan</td>
<td>≥ 4</td>
</tr>
</tbody>
</table>

SMN2 – Survival motor neuron 2.

Clinical Efficacy
The efficacy of Evrysdi for the treatment of patients with infantile-onset (Type 1) and later-onset (Type 2 and 3) spinal muscular atrophy were evaluated in two pivotal clinical trials. FIREFISH was an open-label, two-part study designed to investigate the efficacy, safety, pharmacokinetics, and pharmacodynamics of Evrysdi in patients with Type 1 spinal muscular atrophy who had symptom onset between 28 days and 3 months of age. Genetic confirmation of homozygous deletion or compound heterozygosity predictive or loss of function of the SMN1 gene was required. Patients had two SMN2 gene copies. In Part 1 of the trial, the median age at enrollment was 6.7 months. For this population, of the patients who received the recommended dosage of Evrysdi (0.2 mg/kg QD), 41% of patients (n = 7/17) were able to sit independently for ≥ 5 seconds after 12 months of treatment. After a minimum of 23 months of Evrysdi therapy, 81% of patients (n = 17/21) were alive without permanent ventilation. SUNFISH was a two-part, multicenter trial that assessed the efficacy, safety, pharmacokinetics, and pharmacodynamics of Evrysdi in patients with later-onset (Type 2 or Type 3) spinal muscular atrophy. Most patients (90.2%) had three SMN2 gene copies; 7.8% and 2.0% of patients had four and two SMN2 gene copies, respectively. Part 2 of the study involved 180 nonambulatory patients who were randomized to receive Evrysdi at the FDA-approved dose or placebo. The change from baseline in the Motor Function Measure-32 Items (MFM-32) total score at Month 12 showed a clinically meaningful and statistically significant difference between patients given Evrysdi vs. placebo (P = 0.0156). Also, the change from baseline in total score of the Revised Upper Limb Module (RULM) at Month 12 was statistically superior for Evrysdi vs. placebo (P = 0.0469).

Guidelines
Evrysdi is not addressed in guidelines. The Spinal Muscular Atrophy Newborn Screening Multidisciplinary Working Group is comprised of clinicians and geneticists with expertise in spinal muscular atrophy who developed a treatment algorithm in 2018 for infants who have positive results from a newborn screening test for spinal muscular atrophy. Spinal muscular atrophy Types 1 and 2 comprise a large majority of spinal muscular atrophy cases and account for the majority of patients who screen positively for spinal muscular atrophy and have three or fewer SMN2 gene copies. The Working Group unanimously recommends immediate treatment for these patients to achieve a maximal response to treatment. The NURTURE trial with Spinraza that involved presymptomatic infants who had either two or three SMN2 gene copies supports this recommendation. Treatment recommendations for patients who screen positive for spinal muscular atrophy and have only one SMN2 gene copy is more complicated. It is likely that patients with only one SMN2 gene copy will likely by symptomatic at birth and the physician should determine if treatment is warranted. 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. It is assumed that the recommendation stands that patients with five or more SMN2 gene copies should not be treated immediately but screened for symptoms.

Safety
Based on animal data, Evrysdi may cause fetal harm if given to a pregnant women. 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.

Conditions Not Covered
Complete Paralysis of All Limbs / Permanent Ventilator Dependence
Data are needed to determine if this patient population with advanced spinal muscular atrophy would derive benefits from Evrysdi.

References

1. Evrysdi™ oral solution [prescribing information]. South San Francisco, CA; Genentech (a Member of the Roche Group); August 2020.

“Cigna Companies” refers to operating subsidiaries of Cigna Corporation. All products and services are provided exclusively by or through such operating subsidiaries, including Cigna Health and Life Insurance Company, Connecticut General Life Insurance Company, Cigna Behavioral Health, Inc., Cigna Health Management, Inc., QualCare, Inc., and HMO or service company subsidiaries of Cigna Health Corporation. The Cigna name, logo, and other Cigna marks are owned by Cigna Intellectual Property, Inc. © 2021 Cigna.