



## Prior Authorization Spinal Muscular Atrophy – Evrysdi® (risdiplam oral solution)

### Table of Contents

National Formulary Medical Necessity .....	1
Conditions Not Covered.....	3
Background.....	3
References .....	5
Revision History .....	6

### Product Identifier(s)

64714

#### 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.

### National Formulary Medical Necessity

**Cigna covers risdiplam products (Evrysdi®) as medically necessary when the following criteria are met for FDA Indications or Other Uses with Supportive Evidence:**

Prior Authorization is recommended for prescription benefit coverage of Evrysdi. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of individuals treated with Evrysdi as well as the monitoring required for adverse events and long-term efficacy, approval requires Evrysdi to be prescribed by or in consultation with a physician who specializes in the condition being treated. For certain criteria, verification is required as noted by **[verification required by prescriber]**. All reviews will be forwarded to the Medical Director for evaluation.

**Documentation:** Documentation is required where noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, laboratory tests, claims records, and/or other information. Subsequent coverage reviews for a individual who has previously met the documentation requirements and related criteria in the *Spinal Muscular Atrophy – Evrysdi Prior Authorization Policy* through the Coverage Review Department, and who is requesting reauthorization, the criteria utilized do NOT require re-

submission of documentation for reauthorization, except for the criterion requiring documentation of response or benefit to Evrysdi therapy.

FDA Indication(s)

1. **Spinal Muscular Atrophy – Treatment.** Approve if the individual meets ONE of the following criteria (A or B):
  - A) **Initial Therapy.** Approve for 4 months if the individual meets the following criteria (i, ii, iii, iv, v, vi, vii, and viii):
    - i. Individual is  $\geq 2$  months to  $\leq 25$  years of age; AND
    - ii. Individual has had a 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 **[documentation required]**; AND
    - iii. Individual meets both of the following (a and b):
      - a) Individual has two to four survival motor neuron 2 (SMN2) gene copies **[documentation required]**; AND
      - b) According to the prescriber, the individual has objective signs consistent with spinal muscular atrophy Types 1, 2, or 3 **[documentation required]**; AND
    - iv. For a individual currently receiving or who has received prior treatment with Spinraza® (nusinersen injection for intrathecal use), the prescriber attests that further therapy with Spinraza will be discontinued; AND
    - v. Individual has not received Zolgensma (onasemnogene abeparvovec-xioi suspension for intravenous infusion) in the past **[verification required by prescriber]**; AND  
Note: Verify through claims history that the individual has NOT previously received Zolgensma AND, if no claim for Zolgensma is present, the prescriber must attest that the individual has not previously received Zolgensma.
    - vi. Females of current reproductive potential must have the prescriber confirm BOTH of the following (a and b):
      - a) Individual is not currently pregnant; AND
      - b) Effective contraception will be utilized during treatment and for 1 month after the last Evrysdi dose; AND
    - vii. Dosing of Evrysdi meets ONE of the following based on the current (within the past 1 month) kg weight (a, b, or c):
      - a) 0.2 mg/kg once daily if the individual is 2 months to  $< 2$  years of age; OR
      - b) 0.25 mg/kg once daily for individuals  $\geq 2$  years of age who weigh  $< 20$  kg; OR
      - c) 5 mg once daily for individuals  $\geq 2$  years of age who weigh  $\geq 20$  kg; AND
    - viii. Medication is prescribed by a physician who has consulted with or who specializes in the management of individuals with spinal muscular atrophy and/or neuromuscular disorders; OR
  - B) **Individual is Currently Receiving Evrysdi.** Approve for 4 months if the individual meets all of the following criteria (i, ii, iii, iv, v, vi, vii, and viii):
    - i. Individual has had a 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 **[documentation required]**; AND
    - ii. Individual meets BOTH of the following (a and b):
      - a) Individual has two to four survival motor neuron 2 (SMN2) gene copies **[documentation required]**; AND
      - b) According to the prescriber, the individual has objective signs consistent with spinal muscular atrophy Types 1, 2, or 3 **[documentation required]**; AND
    - iii. For a individual currently receiving or who has received prior treatment with Spinraza (nusinersen injection for intrathecal use), the prescriber attests that further therapy with Spinraza will be discontinued; AND
    - iv. Individual has NOT received Zolgensma (onasemnogene abeparvovec-xioi suspension for intravenous infusion) in the past **[verification required by the prescriber]**; AND

Note: Verify through claims history that the individual has NOT previously received Zolgensma AND, if no claim for Zolgensma is present, the prescriber must attest that the individual has not previously received Zolgensma.

- v. Females of current reproductive potential must have the prescriber confirm BOTH of the following (a and b):
  - a) Individual is not currently pregnant; AND
  - b) Effective contraception will be utilized during treatment and for 1 month after the last Evrysdi dose; AND
- vi. Dosing of Evrysdi meets ONE of the following based on the current (within the past 1 month) kg weight (a, b, or c):
  - a) 0.2 mg/kg if the individual is 2 months to < 2 years of age; OR
  - b) 0.25 mg/kg for individuals  $\geq$  2 years of age who weigh < 20 kg; OR
  - c) 5 mg for individuals  $\geq$  2 years of age who weigh  $\geq$  20 kg; AND
- vii. Medication is prescribed by a physician who has consulted with or who specializes in the management of individuals with spinal muscular atrophy and/or neuromuscular disorders; AND
- viii. According to the prescriber, the individual has responded to Evrysdi and continues to have benefit from ongoing Evrysdi therapy by the most recent (within the past 4 months) objective measurement and/or assessment tool **[documentation required]**.

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 test results suggest benefits, reduced need for respiratory support, decrease in the frequency of respiratory infections or complications, and/or prevention of permanent assisted ventilation).

## 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.** Data are needed to determine if this individual population with advanced spinal muscular atrophy would derive benefits from Evrysdi.
2. **Individual has Permanent Ventilator Dependence.** Data are needed to determine if this individual population with advanced spinal muscular atrophy would derive benefits from Evrysdi.

## Background

### Overview

Evrysdi, a survival motor neuron 2 (SMN2) splicing modifier, is indicated for the **treatment of spinal muscular atrophy** in patients 2 months of age and older.<sup>1</sup>

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  $\geq$  2 years of age and < 20 kg
- 5 mg for patients  $\geq$  2 years of age and  $\geq$  20 kg

### 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.<sup>2-5</sup> The reduced levels of survival motor neuron (SMN) protein causes degeneration of lower motor neurons.<sup>5</sup> Although the condition is a multisystem disorder, it is clinically characterized by progressive muscle weakness and atrophy. Patients have difficulties with

ambulation, head control, feeding and respiration. Cognitive development is not impacted. 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 20,000 children and adults in the US may be impacted.<sup>5</sup> 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.<sup>2-5</sup> 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. Gene deletion testing for spinal muscular atrophy can be performed at many diagnostic laboratories. Table 1 describes disease types. A different manner of categorization classifies the main three most common types as follows: Type 1 patients are “non-sitters”, Type 2 patients are “sitters”, and Type 3 patients are “walkers”.<sup>3,5</sup>

**Table 1. Types of Spinal Muscular Atrophy.<sup>2-5</sup>**

SMA Type	Age at Onset	Features/Clinical Presentation	Lifespan	SMN2 Copy Gene 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
3	> 18 months	Walks independently but may lose this ability as the disease progresses.	Normal	3 to 4

**Table 1 (continued). Types of Spinal Muscular Atrophy.<sup>2-5</sup>**

SMA Type	Age at Onset	Features/Clinical Presentation	Lifespan	SMN2 Copy Gene Number
4	Adulthood	Walk until adulthood.	Normal lifespan	≥ 4

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

Besides Evrysdi, other therapies are available. **Spinraza**<sup>®</sup> (nusinersen injection for intrathecal use), a SMN2-directed antisense oligonucleotide, is indicated for the treatment of spinal muscular atrophy in pediatric and adult patients.<sup>6</sup> 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**<sup>®</sup> (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 SMN1 gene.<sup>7</sup> 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.

### 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 is being evaluated in two ongoing pivotal clinical trials.<sup>1,10</sup> **FIREFISH** is 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.<sup>1</sup>

Genetic confirmation of homozygous deletion or compound heterozygosity predictive or loss of function of the SMN1 gene was required for trial entry. 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) [n = 17], many patients gained improvements in the ability to sit for at least 5 seconds independently, as well as in the percentages of patients who were alive without permanent ventilation.

**SUNFISH** is a two-part, multicenter trial assessing 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. Benefits were noted at Month 12 in motor function as well as in upper limb motor performance. Of note, in general, the onset of effect with Evrysdi was observed after approximately 4 months of therapy.

### 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.<sup>8</sup> Spinal muscular atrophy Types 1 and 2 comprise a large majority of cases and account for many patients who screen positively for spinal muscular atrophy with three or fewer SMN2 gene copies. Immediate treatment is recommended in patients with two or three SMN2 gene copies. 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 be symptomatic at birth and the physician should determine if treatment is warranted.<sup>8</sup> 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.<sup>9</sup> Also, 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.<sup>1</sup> 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.

## References

1. Evrysdi® oral solution [prescribing information]. South San Francisco, CA; Genentech (a Member of the Roche Group); April 2021.
2. Arnold ES, Fischbeck KH. Spinal muscular atrophy. *Handb Clin Neurol*. 2018;148:591-601.
3. Prior TW, Leach ME, Finanger E. Spinal Muscular Atrophy. 2000 Feb 24 [Updated 2019 Nov 14]. In: Adam MP, Ardinger HH, Pagon RA, et al, editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2020. Available at: <https://www.ncbi.nlm.nih.gov/books/NBK1352/>. Accessed on July 14, 2021.
4. Mercuri E, Finkel RS, Muntoni F, et al. Diagnosis and management of spinal muscular atrophy: Part 1: recommendations for diagnosis, rehabilitation, orthopedic and nutritional care. *Neuromuscul Disord*. 2018;28(2):103-115.
5. Yeo CJJ, Darras BT. Overturning the paradigm of spinal muscular atrophy as just a motor neuron disease. *Pediatr Neurol*. 2020;109:12-19.
6. Spinraza® intrathecal injection [prescribing information]. Cambridge, MA: Biogen; June 2020.
7. Zolgensma® intravenous infusion [prescribing information]. Bannockburn, IL: AveXis; March 2021.
8. Glascock J, Sampson J, Haidet-Phillips A, et al. Treatment algorithm for infants diagnosed with spinal muscular atrophy through newborn screening. *J Neuromuscul Dis*. 2018;5:145-158.
9. Glascock J, Sampson J, Connolly AM, et al. Revised recommendations for the treatment of infants diagnosed with spinal muscular atrophy via newborn screening who have 4 copies of SMN2. *J Neuromuscul Dis*. 2020;7(2):97-100.
10. Baranello G, Darras BT, Day JW, et al, for the FIREFISH Working Group. Risdiplam in type 1 spinal muscular atrophy. *N Engl J Med*. 2021;384(10):915-923.

## Revision History

Type of Revision	Summary of Changes	Review Date
Annual Revision	<b>Spinal Muscular Atrophy – Treatment:</b> Removed the criteria that required that the patient does not have evidence of hepatic impairment according to the prescriber in the criteria regarding initial therapy and for patients currently receiving Evrysdi. In the criteria in which the patient is currently receiving Evrysdi, for that criteria which states that “according to the prescriber, the patient has responded to Evrysdi or continues to have benefit from ongoing Evrysdi therapy by the most recent (within the past 4 months) objective measurement and/or assessment tool” the “or” was changed to “and”. To the examples listed in the note regarding this criteria, regarding bulbar function test results the phrase “suggest benefits” was added. Also, the example of “decrease in the frequency of respiratory infections or complications” was added.	07/07/2021

“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.