

PRIOR AUTHORIZATION POLICY

POLICY: Spinal Muscular Atrophy – Evrysdi Prior Authorization Policy

- Evrysdi® (risdiplam oral solution – Genentech/Roche)

REVIEW DATE: 11/01/2023

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 – 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

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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.

POLICY STATEMENT

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 patients treated with Evrysdi as well as the monitoring required for adverse events and long-term efficacy, approval requires Evrysdi to be prescribed by a physician who has consulted with or who specializes in the condition. For certain criteria, verification is required as noted by **[verification in claims history required]**. In the criteria for Evrysdi, as appropriate, an asterisk (*) is noted next to the specified gender. In this context, the specified gender is defined as follows: females are defined as individuals with the biological traits of a woman, regardless of the individual's gender identity or gender expression. All reviews will be forwarded to the Medical Director for evaluation.

Automation: None.

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. In subsequent coverage reviews for a patient 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 resubmission of documentation for reauthorization, except for the criterion requiring documentation of response or benefit to Evrysdi therapy.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Evrysdi is recommended in those who meet the following criteria:

FDA-Approved Indication

1. Spinal Muscular Atrophy – Treatment. Approve if the patient meets ONE of the following criteria (A or B):

A) Initial Therapy. Approve for 4 months if the patient meets all of the following criteria (i, ii, iii, iv, v, vi, vii, and viii):

i. Baseline motor ability assessment that suggests spinal muscular atrophy (based on age, motor ability, and development) has been performed from one of the following exams (a, b, c, d, e, f, or g) **[documentation required]**:

a) Bayley Scales of Infant and Toddler Development; OR

b) Children’s Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND); OR

c) Hammersmith Functional Motor Scale Expanded (HFMSSE); OR

d) Hammersmith Infant Neurological Exam Part 2 (HINE-2); OR

e) Motor Function Measure-32 Items (MFM-32); OR

f) Revised Upper Limb Module (RULM) test; OR

g) World Health Organization motor milestone scale; AND

ii. Patient has had a genetic test confirming the diagnosis of spinal muscular atrophy with bi-allelic pathogenic variants in the survival motor neuron 1 (SMN1) gene **[documentation required]**; AND

Note: Pathogenic variants may include homozygous deletion, compound heterozygous mutation, or a variety of other rare mutations.

iii. Patient meets one of the following criteria (a or b):

a) Patient has two or three survival motor neuron 2 (SMN2) gene copies **[documentation required]**; OR

b) Patient meets both of the following ([1] and [2]):

(1) Patient has four survival motor neuron 2 (SMN2) gene copies **[documentation required]**; AND

(2) Patient has objective signs consistent with spinal muscular atrophy Types 1, 2, or 3 **[documentation required]**; AND

iv. For a patient currently receiving or who has received prior treatment with Spinraza (nusinersen intrathecal injection), the prescribing physician confirms that further therapy with Spinraza will be discontinued; AND

v. Patient has not received Zolgensma (onasemnogene abeparvovec-xioi intravenous infusion) in the past **[verification in claims history required]**; AND

Note: Verify through claims history that the patient has NOT previously received Zolgensma. If no claim for Zolgensma is present, the prescribing physician confirms that the patient has not previously received Zolgensma.

vi. According to the prescribing physician, a female* patient of reproductive potential must meet both the following criteria (a and b):

a) Patient 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 criteria based on the current (within the past 1 month) kg weight of the patient (a, b, c, or d):
 - a) 0.15 mg/kg once daily if the patient is < 2 months of age; OR
 - b) 0.2 mg/kg once daily if the patient is 2 months to < 2 years of age; OR
 - c) 0.25 mg/kg once daily if the patient is \geq 2 years of age and weighs < 20 kg; OR
 - d) 5 mg once daily if the patient is \geq 2 years of age and weighs \geq 20 kg; AND
 - viii. The medication is prescribed by a physician who has consulted with a specialist or who specializes in the management of patients with spinal muscular atrophy and/or neuromuscular disorders; OR
- B) Patient Currently Receiving Evrysdi.** Approve for 4 months if the patient meets all of the following criteria (i, ii, iii, iv, v, vi, vii, and viii):
- i. Patient has had a genetic test confirming the diagnosis of spinal muscular atrophy with bi-allelic pathogenic variants in the survival motor neuron 1 (SMN1) gene **[documentation required]**; AND
Note: Pathogenic variants may include homozygous deletion, compound heterozygous mutation, or a variety of other rare mutations.
 - ii. Patient meets one of the following criteria (a or b):
 - a) Patient has two or three survival motor neuron 2 (SMN2) gene copies **[documentation required]**; OR
 - b) Patient meets both of the following criteria [(1) and (2)]:
 - (1) Patient has four survival motor neuron 2 (SMN2) gene copies **[documentation required]**; AND
 - (2) Patient has objective signs consistent with spinal muscular atrophy Types 1, 2, or 3 **[documentation required]**; AND
 - iii. For a patient currently receiving or who has received prior treatment with Spinraza (nusinersen intrathecal injection), the prescribing physician confirms that further therapy with Spinraza will be discontinued; AND
 - iv. Patient has not received Zolgensma (onasemnogene abeparvovec-xioi intravenous infusion) in the past **[verification in claims history required]**; AND
Note: Verify through claims that the patient has NOT previously received Zolgensma. If no claim for Zolgensma is present, the prescribing physician confirms that the patient has not previously received Zolgensma.
 - v. According to the prescribing physician, a female* patient of reproductive potential must meet both the following criteria (a and b):
 - a) Patient 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 criteria based on the current (within the past 1 month) kg weight of the patient (a, b, c, or d):
 - a) 0.15 mg/kg once daily if the patient is < 2 months of age; OR
 - b) 0.2 mg/kg once daily if the patient is 2 months to < 2 years of age; OR
 - c) 0.25 mg/kg once daily if the patient is \geq 2 years of age and weighs < 20 kg; OR
 - d) 5 mg once daily if the patient is \geq 2 years of age and weighs \geq 20 kg; AND
 - vii. The medication is prescribed by a physician who has consulted with a specialist or who specializes in the management of patients with spinal muscular atrophy and/or neuromuscular disorders; AND
 - viii. Patient must meet one of the following criteria (a or b):
 - a) Patient must have had a positive clinical response (for example, improvement or stabilization) from pretreatment baseline status (i.e., within the past 4 months) with Evrysdi in one of the following exams [(1), (2), (3), (4), (5), (6), or (7)] **[documentation required]**:
 - (1) Bayley Scales of Infant and Toddler Development; OR

- (2) Children’s Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND); OR
 - (3) Hammersmith Functional Motor Scale Expanded (HFMSSE); OR
 - (4) Hammersmith Infant Neurological Exam Part 2 (HINE-2); OR
 - (5) Motor Function Measure-32 Items (MFM-32); OR
 - (6) Revised Upper Limb Module (RULM) test; OR
 - (7) World Health Organization motor milestone scale; OR
- b) According to the prescribing physician, the patient has responded to Evrysdi and continues to benefit from ongoing Evrysdi therapy by the most recent (i.e., within the past 4 months) physician monitoring/assessment tools **[documentation required]**.
Note: Examples include pulmonary function tests showing improvement, bulbar function test results suggesting benefits, reduced need for respiratory support, decrease in the frequency of respiratory infections or complications, and/or prevention of permanent assisted ventilation.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Evrysdi is not recommended in the following situations:

1. **Patient 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. **Patient has Permanent Ventilator Dependence.** Data are needed to determine if this patient population with advanced spinal muscular atrophy would derive benefits from Evrysdi.
3. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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