PRIOR AUTHORIZATION POLICY

POLICY: Spinal Muscular Atrophy – Evrysdi Prior Authorization Policy
- Evrysdi® (risdiplam oral solution – Genentech/Roche)

REVIEW DATE: 08/12/2020; selected revision 09/30/2020 and 11/18/2020

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.1

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

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. 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.5 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 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”.3,5

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

<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; 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>1</td>
<td>&lt; 6 months</td>
<td>Poor muscle tone, lack of movement, and 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>Before 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>
</tbody>
</table>

Table 1 (continued). Types of Spinal Muscular Atrophy.2-5
SMA – Spinal muscular atrophy; SMN2 – Survival motor neuron 2.

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. 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 SMN1 gene. 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. 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. 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. 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. In 2020, the Working Group updated recommendations that infants diagnosed with spinal muscular atrophy via newborn screening...
screening with four SMN2 gene copies should receive immediate treatment. Also, patients with five (or more) SMN2 gene copies should observed and 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. Because the efficacy and safety of Evrysdi in patients with hepatic impairment have not been studied, avoid use of this agent in patients with impaired hepatic function.

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 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.

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. 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 re-submission 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 Indications

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, viii, and ix):
      i. Patient is ≥ 2 months to ≤ 25 years of age; AND
      ii. Patient 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. Patient meets both of the following (a and b):
         a) Patient has two to four survival motor neuron 2 (SMN2) gene copies [documentation required]; AND
         b) According to the prescriber, the 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 injection for intrathecal use), the prescriber attests that further therapy with Spinraza will be discontinued; AND

v. Patient 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 patient has NOT previously received Zolgensma AND, if no claim for Zolgensma is present, the prescriber must attest that the patient has not previously received Zolgensma.

vi. Females of current reproductive potential must have the prescriber confirm BOTH of the following (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. According to the prescriber, the patient does not have evidence of hepatic impairment; AND

viii. 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 patient is 2 months to < 2 years of age; OR
   b) 0.25 mg/kg once daily for patients ≥ 2 years of age who weigh < 20 kg; OR
   c) 5 mg once daily for patients ≥ 2 years of age who weigh ≥ 20 kg; AND

ix. Medication is prescribed by a physician who has consulted with or who specializes in the management of patients with spinal muscular atrophy and/or neuromuscular disorders; OR

B) Patient is Currently Receiving Evrysdi. Approve for 4 months if the patient meets all of the following criteria (i, ii, iii, iv, v, vi, vii, viii, and ix):

i. Patient 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. Patient meets BOTH of the following (a and b):
   a) Patient has two to four survival motor neuron 2 (SMN2) gene copies [documentation required]; AND
   b) According to the prescriber, the 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 injection for intrathecal use), the prescriber attests that further therapy with Spinraza will be discontinued; AND

iv. Patient 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 patient has NOT previously received Zolgensma AND, if no claim for Zolgensma is present, the prescriber must attest that the patient has not previously received Zolgensma.

v. Females of current reproductive potential must have the prescriber confirm BOTH of the following (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. According to the prescriber, the patient does not have evidence of hepatic impairment; 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 if the patient is 2 months to < 2 years of age; OR
   b) 0.25 mg/kg for patients ≥ 2 years of age who weigh < 20 kg; OR
c) 5 mg for patients ≥ 2 years of age who weigh ≥ 20 kg; AND

viii. Medication is prescribed by a physician who has consulted with or who specializes in the management of patients with spinal muscular atrophy and/or neuromuscular disorders; AND

ix. 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 [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 results, reduced need for respiratory support, 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.

REFERENCES

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

<table>
<thead>
<tr>
<th>Type of Revision</th>
<th>Summary of Changes</th>
<th>Review Date</th>
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<tbody>
<tr>
<td>New Policy</td>
<td>--</td>
<td>08/12/2020</td>
</tr>
<tr>
<td>Selected Revision</td>
<td><strong>Spinal Muscular Atrophy – Treatment:</strong> For a patient using Evrysdi for spinal muscular atrophy (treatment) who are currently receiving Evrysdi, the requirement that the patient is ≥ 2 months of age and ≤ 25 years of age was removed. Also, regarding the criteria pertaining to Spinraza, wording was added to include not only those who have received prior treatment with Spinraza, but also those “currently receiving” the therapy; it should be attested that the therapy will not be further given with Spinraza use. A slight change was made to the documentation statement. For this related criterion regarding patients currently receiving Evrysdi therapy, it was specified that “the most recent (within the last 4 months)” objective measurement and/or assessment tool will be utilized. <strong>Documentation:</strong> Wording was added that for 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 re-submission of documentation for reauthorization, except for the criterion requiring documentation of response or benefit to Evrysdi therapy.</td>
<td>09/30/2020</td>
</tr>
<tr>
<td>Selected Revision</td>
<td><strong>Spinal Muscular Atrophy – Treatment:</strong> The criteria that requires the medication to be prescribed by or in consultation with a physician who specializes in the management of patients with spinal muscular atrophy and/or neuromuscular disorders was changed to “medication is prescribed by a physician who has consulted with or who specializes in the management of patients with spinal muscular atrophy and/or neuromuscular disorders”.</td>
<td>11/18/2020</td>
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