Introduction

Spinal muscular atrophy (SMA) is a rare disease that leads to muscle weakness and atrophy. SMA affects the muscles of the limbs and trunk. SMA is caused by changes to the survival motor neuron 1 gene (SMN1). This gene creates a protein called the survival motor neuron (SMN) protein. Too little of the SMN protein leads to muscle weakness that gets worse over time and muscles that waste away (atrophy). There are different types of SMA. Type 1 SMA, also known as Werdnig-Hoffman disease or infantile SMA, is the most severe form. Symptoms usually start before 6 months of age. The chance of survival to one year of age is 50 percent. Less severe forms are Type 2, also known as Dubowitz disease, and Type 3, or Kugelberg-Welander disease. Spinraza® (nusinersen) and Zolgensma® (onasemnogene abeparvovec-xioi) are two treatments the Food and Drug Administration has approved for SMA. This policy discusses when the use of Spinraza® and Zolgensma® may be considered medically necessary.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Medical Necessity</th>
</tr>
</thead>
</table>
| **Spinraza® (nusinersen)**                 | **Spinraza® (nusinersen) may be considered medically necessary for the treatment of spinal muscular atrophy (SMA) when:**  
• Patient has a diagnosis of SMA Type 1, 2 or 3 attributed to the bi-allelic mutations of survival motor neuron 1 (SMN1) gene documented by genetic testing  
  
**Note:** Although Types 2 and 3 manifest in childhood, treatment may be continued throughout the patient’s lifetime.  
**Note:** The recommended dosage is 12 mg (5mL) per administration. Treatment with Spinraza® should be initiated with 4 loading doses. The first 3 loading doses should be administered at 14-day intervals. The 4th loading dose should be administered 30 days after the 3rd dose. The maintenance dose for Spinraza® is administered once every 4 months thereafter. |
| **Zolgensma® (onasemnogene abeparvovec-xioi)** | **Zolgensma® (onasemnogene abeparvovec-xioi) may be considered medically necessary for the treatment of spinal muscular atrophy (SMA) when:**  
• Patient is less than 2 years of age at the time of infusion  
  AND  
• Has a diagnosis of SMA attributed to the bi-allelic mutations of survival motor neuron 1 (SMN1) gene documented by genetic testing  
  AND  
• Documented genetic test confirms 3 or fewer copies of the SMN2 gene  
  AND  
• Patient does not have advanced SMA  
  AND  
• Baseline anti-adeno-associated virus serotype 9 (AAV9) antibody levels are ≤ 1:50  
  AND  
• Prescribed by a neurologist with expertise treating SMA  
  AND  
• Zolgensma is administered as a one-time infusion  
  
**Note:** The recommended dosage is $1.1 \times 10^{14}$ vector genomes per kg of body weight administered as an intravenous infusion over 60 minutes. |
<table>
<thead>
<tr>
<th>Drug</th>
<th>Investigational</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Spinraza® (nusinersen)</strong></td>
<td>All other uses of Spinraza® (nusinersen) for conditions not outlined in this policy are considered investigational, including but not limited to:</td>
</tr>
<tr>
<td></td>
<td>• SMA that is not attributed to the bi-allelic mutations of SMN1 gene</td>
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<td></td>
<td>• SMA type 4 (adult onset)</td>
</tr>
<tr>
<td></td>
<td>• Spinraza® use after Zolgensma infusion</td>
</tr>
<tr>
<td><strong>Zolgensma® (onasemnogene abeparvovec-xioi)</strong></td>
<td>All other uses of Zolgensma® (onasemnogene abeparvovec-xioi) for conditions not outlined in this policy are considered investigational, including but not limited to:</td>
</tr>
<tr>
<td></td>
<td>• SMA that is not attributed to the bi-allelic mutations of SMN1 gene</td>
</tr>
<tr>
<td></td>
<td>• Patient’s with 4 or more copies of the SMN2 gene</td>
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</table>

<table>
<thead>
<tr>
<th>Length of Approval</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial authorization</td>
<td>Spinraza® (nusinersen) may be approved up to six months.</td>
</tr>
<tr>
<td></td>
<td>Zolgensma® (onasemnogene abeparvovec-xioi) may be approved as a one-time infusion.</td>
</tr>
<tr>
<td>Re-authorization criteria</td>
<td>Future re-authorization of Spinraza® (nusinersen) may be approved up to 12 months in duration when clinical benefit/response at the time of re-authorization based on evidence show continued benefit.</td>
</tr>
<tr>
<td></td>
<td>Future re-authorization of Zolgensma® (onasemnogene abeparvovec-xioi) beyond a one-time infusion is considered investigational.</td>
</tr>
</tbody>
</table>
Documentation Requirements

- Initial approval requires chart notes documenting the diagnosis and genetic testing documenting bi-allelic mutations of SMN1 gene and the copies of SMN2 gene
- Spinraza® reauthorization requires chart notes documenting progress, including functional measures appropriate to the patient’s current abilities, eg, ambulation, arm strength or pulmonary function.

Coding

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>J2326</td>
<td>Injection, nusinersen (Spinraza®), 0.1 mg</td>
</tr>
<tr>
<td>J3590</td>
<td>Unclassified biologics (use this code only to report Zolgensma®)</td>
</tr>
</tbody>
</table>

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Related Information

Benefit Application

This policy is managed through the medical benefit.

Consideration of Age

Age limits specified in this policy for Zolgensma® are determined according to the FDA-approved indication. The use of Spinraza® for SMA type 1, 2, and 3 is based on the clinical trial experience as described in the full prescribing information of the FDA label. The controlled trial was a study of infantile-onset SMA patients. The patients in these studies had or were likely to develop type 1, 2, or 3 SMA.
Availability

Zolgensma® is only available at certified treatment centers. Information on certified treatment centers is available by emailing treatments@curesma.org.

Evidence Review

Disease Background

Spinal muscular atrophy (SMA) is a rare recessive neurodegenerative disease that leads to muscle weakness and atrophy of the voluntary muscles of the limbs and trunk, due to the progressive loss of anterior horn cells of the spinal cord and brainstem nuclei. SMA has an incidence of about 1:10,000 live births and is the leading genetic cause of infant death. It has a carrier frequency estimated to be between 1:40 to 1:60.

SMA is caused by the homozygous deletion of the survival motor neuron 1 gene (SMN1), which encode stable survival motor neuron (SMN) protein. The absence of enough SMN leads to increasing motor neuron dysfunction and progressive muscle weakness and atrophy. Cases are classified based on their severity and maximal achieved motor abilities, inversely correlating with the age of onset as well as the number of survival motor neuron 2 gene (SMN2) copies present. SMN2 encodes for SMN proteins that are less stable than those produced by SMN1 and do not have as lasting an impact on motor neuron function. SMN1 and SMN2 are nearly identical and encode the same protein. The critical sequence difference between the two genes is a single nucleotide in exon 7, which is thought to be an exon splice enhancer.

Type 1 SMA, also known as Werdnig-Hoffman disease or infantile SMA, is the most severe with symptomatic onset usually before 6 months and the probability of survival at 1 year is 50%. Type 2 SMA is also called intermediate SMA or Dubowitz disease while type 3 SMA is also called juvenile SMA or Kugelberg-Welander disease, and both have slightly older age of onsets and more varied disease progression. Type 4 SMA is an adult onset form of SMA that is usually not symptomatic until later in life and rarely affects life expectancy.
Table 1. Clinical Classification of SMA

<table>
<thead>
<tr>
<th>SMA Type</th>
<th>Age of Onset</th>
<th>Highest Achieved Motor Function</th>
<th>Natural Age of Death</th>
<th>Typical Number of SMN2 Copies</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Prenatal/fetal</td>
<td>None</td>
<td>&lt; 6 months</td>
<td>1</td>
</tr>
<tr>
<td>I</td>
<td>&lt; 6 months</td>
<td>Sit with support only</td>
<td>&lt; 2 years</td>
<td>2</td>
</tr>
<tr>
<td>II</td>
<td>6 – 18 months</td>
<td>Sit independently</td>
<td>&gt; 2 years</td>
<td>3 or 4</td>
</tr>
<tr>
<td>III</td>
<td>&gt; 18 months</td>
<td>Walk independently</td>
<td>Adulthood</td>
<td>3 or 4</td>
</tr>
<tr>
<td>IV</td>
<td>Adult (20s-30s)</td>
<td>Walk through adulthood</td>
<td>Adult</td>
<td>4 to 8</td>
</tr>
</tbody>
</table>

Spinraza® (nusinersen)

Spinraza® is a SMN2 directed antisense oligonucleotide that increases the production of complete SMN protein by increasing exon 7 inclusion into SMN2 mRNA transcripts (alternative splicing). The resulting protein resembles those produced by SMN1 and is more stable than regular SMN protein produced by SMN2. SMN protein is involved in the maintenance of motor neurons which control muscle movement. This allows SMA patients to achieve motor milestones and improve their functional abilities.

In one clinical study, Spinraza® resulted in platelet levels below the lower limit of normal in 6 of the 56 patients who had normal baseline levels; however none of these patients developed a sustained low platelet count. In two different studies, 17 out of 51 patients and 36 out of 52 patients on Spinraza® had elevated urine protein. Common adverse reactions recorded in infantile SMA patients included lower respiratory infection (43%), upper respiratory infection (39%), and constipation (30%), while common adverse reactions recorded in later onset patients include headache (50%), back pain (41%), and post-lumbar puncture syndrome (41%) and were associated with the intrathecal administration.

Evidence of Efficacy

Currently, there are ten clinical trials that evaluate the use of Spinraza® for SMA treatment, with efficacy endpoints focused on survival, growth parameters, electro-physiology, and motor function. The ENDEAR study, which provided much of the efficacy evidence, was a phase 3 sham procedure controlled study which depicted a 29% reduction in risk of death or permanent ventilation in the nusinersen group compared to the sham procedure controlled group. Mean improvements in motor milestones for the nusinersen group was observable starting at 2
months post treatment initiation with an increased difference from the sham control patients as the study went on.

In another study, the interim analysis of 13 pre-symptomatic patients SMA patients demonstrated that patients treated with nusinersen exceeded expected outcomes with improvements in various motor function and motor milestone measures. Compared to the Pediatric Neuromuscular Clinical Research natural-history studies of SMA patients that received standard of care, patients with type 1 SMA treated with nusinersen had a significant differentiation in age at death or permanent ventilation as well as increased motor function and nerve response. The CS2 and CS12 studies showed additional milestone attainment and maintenance in type 2 and 3 SMA patients who received nusinersen compared to the decline in milestone maintenance commonly seen in SMA patients, with independent walking achieved in three patients and increased mean ambulation. Nusinersen has not been studied in type 4 patients.

**Evidence of Safety**

In the limited studies available, Spinraza® has been shown to be generally safe, with most adverse events associated with the route of administration or the natural progression of SMA. Elevated urine protein and low platelet levels have been observed in a few studies with nusinersen; however the coagulation abnormalities, thrombocytopenia, and renal toxicity associated with antisense oligonucleotides has not been observed with nusinersen though they are still listed as precautions. The majority of adverse events associated with nusinersen were mild to moderate in severity and mirrored events seen in the controlled historical groups, including respiratory distress, respiratory failure, pneumonia, acute respiratory failure, atelectasis, pneumonia aspiration, rhinovirus infection, and cardiorespiratory arrest.

**Zolgensma® (onasemnogene abeparvovec-xioi)**

Zolgensma® is a gene therapy that uses the adeno-associated virus serotype 9 vector (AAV9) to deliver a copy of the SMN gene to the nucleus of the patient’s cells to replace the defective SMN1 gene without modifying the existing DNA of the patient.
Evidence of Efficacy

A Phase I, single-arm, open-label trial evaluated Zolgensma for the treatment of 15 patients with genetically confirmed diagnosis of SMA1, homozygous SMN1 exon 7 deletions, and two copies of SMN2. Subjects were excluded if they had anti-AAV9 antibody titers > 1:50. Of the 15 study patients, the three patients in cohort 1 received a low dose of adeno-associated virus serotype 9 carrying SMN (6.7 x 10^13 vg per kg of body weight) and the 12 patients in cohort 2 received a high dose (2.0 x 10^14 vg per kg of body weight). The mean age of patients at the time of treatment was 6.3 months (range 5.9 to 7.2) in cohort 1 and 3.4 months (range 0.9 to 7.9) in cohort 2. As a result of serum aminotransferase elevations in Patient 1 in cohort 1, which led to a protocol amendment, Patients 2 to 15 received oral prednisolone at a dose of 1 mg per kg per day for approximately 30 days, starting 24 hours before the administration of gene therapy. The gene vector was delivered in normal saline that was infused IV during a period of approximately 60 minutes.

The primary outcome was the determination of safety on the basis of any treatment-related adverse events (AEs) of grade 3 or higher. The secondary outcome was the time until death or the need for permanent ventilatory assistance. Permanent ventilatory assistance was defined as at least 16 hours of respiratory assistance per day continuously for at least 14 days in the absence of an acute, reversible illness or a perioperative state. As of August 7, 2017, all the patients had reached an age of at least 20 months and did not require permanent mechanical ventilation; the median age at their last pulmonary assessment was 30.8 months in cohort 1 and 25.7 months in cohort 2. At 29 months of age, one patient in cohort 1 required permanent ventilation because of hypersalivation. After salivary gland ligation, the requirement for the use of noninvasive ventilation was reduced by 25% to 15 hours per day.

Exploratory outcomes included motor-milestone achievements (particularly, sitting unassisted) and The Children’s Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND) scores. All the patients in cohorts 1 and 2 had increased scores from baseline on the CHOP INTEND scale and maintained these changes during the study. Patients in cohort 2 had mean increases of 9.8 points at 1 month and 15.4 points at 3 months (P<0.001 for both comparisons); 11 patients attained and sustained scores of more than 40 points. No patients in cohort 1 attained any motor milestones. A total of 11 of 12 patients in cohort 2 were able to sit unassisted for at least 5 seconds, 10 for at least 10 seconds, and 9 for at least 30 seconds. A total of 11 achieved head control, 9 could roll over, and 2 were able to crawl, pull to stand, stand independently, and walk independently. Eleven patients attained the ability to speak.
**Evidence of Safety**

As of August 7, 2017, a total of 56 serious adverse events were observed in 13 patients in the two cohorts. Of these, 2 events were treatment-related grade 4 based on laboratory values. Patient 1 in cohort 1 had elevations in serum aminotransferase levels (31 times the ULN for ALT and 14 times the ULN for AST) without other liver-function abnormalities and without clinical manifestations. These elevations were attenuated by prednisolone treatment, which was subsequently administered in the remaining patients. One patient in cohort 2 required additional prednisolone to attenuate elevated serum ALT and AST levels. Of the 241 non-serious adverse events, 3 were deemed to be treatment-related and consisted of asymptomatic elevations in serum aminotransferase levels in 2 patients. The most common adverse events were upper respiratory tract infection (73%), vomiting (53%), constipation (53%), pyrexia (47%), nasal congestion (40%), and gastroesophageal reflux (40%).

**2018 Update**

A literature search from 1/1/17 to 3/30/18 did not reveal new clinical data requiring change to the above criteria. Added reauthorization period and criteria.

**2019 Update**

Added criteria for Zolgensma® (onasemnogene abeparvovec-xioi) which was approved by the FDA in May 2019. Reviewed prescribing information for Spinraza® (nusinersen) and no new information was identified that would change coverage criteria.

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**References**


18. Finkel RS, Mercuri E, Meyer OH, et al. Diagnosis and management of spinal muscular atrophy: Part 2: Pulmonary and acute care; medications, supplements and immunizations; other organ systems; and ethics. Neuromuscul Disord. 2018;28(3):197-207


<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>04/01/17</td>
<td>New policy, approved March 14, 2017. Add to Prescription Drug section. Nusinersen (Spinraza®) may be considered medically necessary to treat SMA when criteria are met; all other uses are considered investigational.</td>
</tr>
<tr>
<td>07/01/17</td>
<td>Coding update; added HCPCS code C9489 (new code effective 7/1/17).</td>
</tr>
<tr>
<td>11/01/17</td>
<td>Interim Review, approved October 10, 2017. Clarified Spinraza® (nusinersen) criteria to include Type 1, 2, and 3 information.</td>
</tr>
<tr>
<td>01/01/18</td>
<td>Coding update; added HCPCS code J2326 (new code effective 1/1/18).</td>
</tr>
<tr>
<td>05/01/18</td>
<td>Annual Review, approved April 3, 2018. Added reauthorization criteria and duration. Removed HCPCS C9489 (it was terminated 1/1/18) and J3490 from policy.</td>
</tr>
<tr>
<td>09/21/18</td>
<td>Minor update. Added Consideration of Age statement.</td>
</tr>
</tbody>
</table>

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U.S. Department of Health and Human Services
200 Independence Avenue SW, Room S09F, HHH Building
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)

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Arabic (Arabic):
كيرم كل المعلومات، يجب أن تكون هذه المعلومات مفيدة لفوكس سلطك أو

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Lakkoofsa bilbilaa 800-722-1471 (TTY: 800-842-5357) ti bilbilaa.

Français (French):
Appelez le 800-722-1471 (TTY: 800-842-5357).

Kreyòl ayisyen (Creole):

Deutsche (German):

Hmoob (Hmong):

Illoko (Ilocano):
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Tagalog (Tagalog): Ang Paunawa na ito ay naglalaman ng mahalagang impormasyon. Ang paunawa na ito ay maaring nagalaman ng mahalagang impormasyon tungkol sa iyong aplikasyon o pagsakop sa pamamagitan ng Premera Blue Cross. Maaaring may mga mahalagang petsa dito sa paunawa. Maaring dapat malaman i ai. Lulukan o iai ni feau e tatau ona e faia ao le'i aulia le faia o le polokalame, Premera Blue Cross, ua e tau fia maua atu i ai. Fa'asamoa o la fia alelie i ai o fa'apito olo'i i ai i lei fa'asilasila taula. Masalo o le aia ni feau e tatau ona e faia ao le'i aulia le aso u leu a ta'i ai le fa'asilasila ina ia e i pe ia ma maas o faia mai ai i le polokalame a le Malo olo'o i ai o Iai. Olo o ia iai ni feau e tatau ona e faia atu i ai. Ii kia fa'asilasila iai i lei fia'ata i le leganae e te malamalama o auna ma se tojiga tupe. Vili u le ilei le telefoni 800-722-1471 (TTY: 800-842-5357).