Pharmacotherapy of Spinal Muscular Atrophy (SMA)

Effective Date: May 1, 2018
Last Revised: Sept. 21, 2018
Replaces: N/A

Related Medical Policies: None

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. Until a new type of drug, Spinraza® (nusinersen), was approved there was no treatment. Less severe forms are Type 2, also known as Dubowitz disease, and Type 3, or Kugelberg-Welander disease. Spinraza is a medication that the Food and Drug Administration has approved for SMA. This policy discusses when the use of Spinraza 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.
### Drug

**Spinraza® (nusinersen)**

**Medical Necessity**

Spinraza® (nusinersen) may be considered medically necessary when:

- Patient has a diagnosis of Spinal Muscular Atrophy (SMA) Type 1, 2 or 3 attributed to the homozygous deletion of SMN1 gene.
  - Testing is necessary to confirm presence of the SMN1 gene deletion
  - Although Types 2 and 3 manifest in childhood, treatment may be continued throughout the patient’s lifetime.

Spinraza® (nusinersen) is investigational for all uses not listed in this policy, including but not limited to:

- Spinal Muscular Atrophy (SMA) that is **not** attributed to a homozygous deletion of SMN1 gene
- SMA type 4 (adult onset)

All other uses of Spinraza® (nusinersen) for conditions not outlined in this policy are considered investigational.

**Note:** Recommended dosing can be found in the Dosage and Quantity Limits section below.

### Approval

<table>
<thead>
<tr>
<th>Criteria</th>
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<tbody>
<tr>
<td><strong>Initial authorization</strong></td>
</tr>
<tr>
<td><strong>Re-authorization criteria</strong></td>
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</table>

### Condition

<table>
<thead>
<tr>
<th>Condition</th>
<th>Dosage and Quantity Limit</th>
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<tbody>
<tr>
<td><strong>Spinal Muscular Atrophy</strong></td>
<td>The recommended dosage is 12mg (5mL) per administration</td>
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<tr>
<td></td>
<td>Initiate Spinraza® (nusinersen) treatment with 4 loading doses:</td>
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<tr>
<td></td>
<td>- The first 3 loading doses should be administered at 14-day intervals</td>
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<td></td>
<td>- The 4th loading dose should be administered 30 days after the 3rd dose</td>
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<td>- A maintenance dose should be administered once every 4 months thereafter</td>
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Documentation Requirements

- Initial approval requires chart notes documenting the diagnosis, including documentation that the patient tests positive for SMN1 deletion.
- 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>HCPCS</td>
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<tr>
<td>J2326</td>
<td>Injection, nusinersen (Spinraza®), 0.1 mg (new code effective 1/1/18)</td>
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</table>

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Related Information

Benefit Application

This policy is managed through the medical benefit.

Consideration of Age

The use of this agent 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.
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.\(^2\) 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\%.\(^2,7\) 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.

Spinraza® (nusinersen)

Spinraza® (nusinersen) 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® (nusinersen) 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® (nusinersen) 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® (nusinersen) for SMA treatment, with efficacy endpoints focused on survival, growth parameters, electro-physiology, and motor function.\(^8\,10\) 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.\(^10\) 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.\(^10\)

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.\(^10\) 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.\(^8\,9\) 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® (nusinersen) 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.

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.

References

## History

<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
</tr>
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<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>
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<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>
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<tr>
<td>01/01/18</td>
<td>Coding update; added HCPCS code J2326 (new code effective 1/1/18).</td>
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<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>
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</table>

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U.S. Department of Health and Human Services
200 Independence Avenue SW, Room 509F, HHH Building
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)

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