Nusinersen (Spinraza™)

Description of Procedure or Service

Spinal muscular atrophy (SMA) is an inherited disorder caused by homozygous deletions or variants in the \textit{SMN1} gene. As a consequence of low levels of SMN protein, the motor neurons in spinal cord degenerate, resulting in atrophy of the voluntary muscles of the limbs and trunk. Nusinersen is a synthetic antisense oligonucleotide designed to bind to a specific sequence in exon 7 of the \textit{SMN2} transcript causing the inclusion of exon 7 in the \textit{SMN2} transcript, leading to production of full length functional SMN protein.

SPINAL MUSCULAR ATROPHY

Spinal muscular atrophy (SMA) is a rare autosomal recessive genetic disorder caused by homozygous deletions or variants in the \textit{SMN1} gene in chromosome 5. This gene is responsible for producing the “survival of motor neuron” protein. As a consequence of low levels of SMN protein, the motoneurons in the spinal cord degenerate, resulting in atrophy of the voluntary muscles of the limbs and trunk. During early development, these muscles are necessary for crawling, walking, sitting up, and head control. The more severe types of SMA can also affect muscles involved in feeding, swallowing, and breathing. The exact role of the SMN protein in motoneurons has not been completely elucidated and levels of the SMN protein required for optimal functioning are unknown. \textit{SMN2} is a nearly identical modifying gene capable of producing compensatory SMN protein. However, 70% to 90% of the transcripts produced from the \textit{SMN2} gene produce a truncated protein that is defective and unstable due to lack of exon 7. Further, humans exhibit variability (range, 0-6) in the number of copies of the \textit{SMN2} gene and copy number is inversely proportional to severity of disease. These factors in tandem lead to wide variability in disease severity.

SMA is classified into 4 main categories (with additional subcategories) based on the age at the onset of symptoms and various motor milestones. Generally, early onset of disease directly correlates to severity of symptom and rate of disease progression. There is no exact marker to classify these categories, and they are not well-distinguished by ICD-10-CM code.

- Type 0: The most severe form of SMA, symptoms can often be seen in the later stages of pregnancy. Fetal movements are less than expected and, after birth, the infant will have little ability to move and may not be able to breathe and swallow independently. Death occurs before the age of 6 months.
- Type I (also called infantile SMA or Werdnig-Hoffman disease and subcategorized as IA, IB and IC): Onset within 6 months of birth and symptoms progress rapidly, and most infants die before 1 year of age from respiratory failure. About 60% of patients with SMA constitute of this phenotype.
- Type II (also called intermediate SMA or Dubowitz disease): Onset within 6 to 18 months with a less severe progression. Typically, a child can sit independently if positioned, but is unable to walk. Many patients will ultimately lose the ability to sit.
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independently. More than 70% of patients live beyond 25 years of age with adequate supportive care.

- Type III (also called Kugelberg-Welander disease and subcategorized as IIIA and IIIB): Onset after 18 months of age. Patients achieve the ability to walk but many will lose this ability later in the course of the disease. Lifespan is not affected, with wide-ranging reduction in muscle strength with a chronic course. The outcome depends primarily on the severity of muscle weakness at presentation rather than age of onset, but earlier onset tends to correlate with greater weakness.

- Type IV (also called adult-onset SMA): Usually presents in the third decade of life. Patients remain ambulatory but may have hip and shoulder girdle weakness mimicking a mild limb-girdle muscular dystrophy.

The prevalence of SMA is estimated to be between 9.1 and 10 per 100,000 live births. In 95% of cases, both copies of the SMN1 exon 7 are absent. The remaining 5% of cases are compound heterozygotes for SMN1 exon 7 deletion and small intragenic variants. The molecular diagnosis of SMA consists of the detection of the absence of exons 7 of the SMN1 gene in the majority of cases.

Treatment
Nusinersen is a modified antisense oligonucleotide (a synthetic genetic material) that binds to a specific sequence in the intron downstream of exon 7 of the SMN2 transcript; nusinersen causes the inclusion of exon 7 in the SMN2 transcript, leading to production of full length functional SMN protein. Prior to approval of nusinersen, there were no treatments approved by the Food and Drug Administration for SMA. Medical management of SMA patients includes respiratory, digestive, and musculoskeletal supportive care.

REGULATORY STATUS
On December 23, 2016, Spinraza™ (nusinersen; Biogen) was approved by the U.S. Food and Drug Administration (FDA) for treatment of pediatric and adult patients with spinal muscular atrophy.

***Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.

Policy

BCBSNC will provide coverage for Nusinersen (Spinraza™) when it is determined to be medically necessary because the medical criteria and guidelines shown below are met.

Benefits Application
This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Nusinersen (Spinraza™) is covered

Initial Therapy
Nusinersen is considered medically necessary for the treatment of spinal muscular atrophy in individuals who meet both criteria A and B:

A. Documentation of confirmatory diagnosis by either:
   1. SMA diagnostic test results confirming 0 copies of SMN1; OR
   2. Molecular genetic testing of 5q SMA for any of the following:
Nusinersen (Spinraza™)

a. homozygous gene deletion; or
b. homozygous conversion mutation; or
c. compound heterozygote;

AND

B. Documentation of either:
1. Genetic testing confirming no more than 2 copies of SMN2; or
2. SMA-associated symptoms before 6 months of age.

Continuation Therapy*
Continuation of treatment with nusinersen beyond 6 months after initiation of therapy, and every 6 months thereafter, is considered medically necessary for the treatment of spinal muscular atrophy when individuals meet both criteria A and B:

A. When initial therapy was determined to meet the above criteria, and
B. When there is documentation of clinically significant improvement in spinal muscular atrophy-associated symptoms (for example, progression, stabilization, or decreased decline in motor function) compared to the predicted natural history trajectory of disease.

*Note: If an individual meets medically necessary criteria, dosing of nusinersen treatment is covered according to the Food and Drug Administration (FDA) product information label. The FDA recommends that a maintenance dose should be administered once every 4 months. As noted above, to continue therapy, medically necessary criteria requires the evaluation and demonstration of nusinersen's clinical effectiveness in the treated individual every 6 months.

When Nusinersen (Spinraza™) is not covered
Use of nusinersen is considered investigational when the criteria above are not met and for all other indications, including but not limited to non-5q-spinal muscular atrophy disorders.

Policy Guidelines

1. Prior to treatment with nusinersen (Spinraza™), members must be evaluated by a board-certified neurologist/pediatric neurologist who is experienced in the diagnosis and management of SMA. The provider requesting prior authorization for nusinersen should also be a board-certified neurologist/pediatric neurologist.

2. Laboratory Testing and Monitoring to Assess Safety:
   At baseline and prior to each dose, obtain a platelet count, coagulation laboratory testing, and quantitative spot urine protein testing.

For individuals who have type 1 (infantile-onset) SMA (symptomatic or presymptomatic) who receive nusinersen, the evidence includes 2 randomized, double-blind, controlled trial (results not yet reported for one) and 1 single-arm open-label study. Relevant outcomes are overall survival, change in disease status, morbid events, functional outcomes, health status measures, quality of life, and treatment-related mortality and morbidity. Trial results in symptomatic patients has shown clinically meaningful improvement in motor milestones as well as event-free survival, which exceeded those seen in the control group, with an acceptable safety profile. The proportion of patients, who met the primary end point responder definition of achieving motor milestones, was 40% in the nusinersen arm compared to 0 in the sham-controlled arm. Further, the hazard ratio for event-free survival was 0.53 in favor of nusinersen versus sham controlled. It is notable, however, that most nusinersen-treated subjects did not achieve the primary end point motor milestone response. Given the limited data on durability of response, long-term safety, and lack of efficacy in substantial number of patients, continued risk-benefit assessment of long-term treatment with nusinersen is necessary. The open-label uncontrolled trial in pre-symptomatic infantile-onset SMA patients found a benefit of early treatment with nusinersen. The evidence is
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sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

To date, there is no evaluable published data on the safety and efficacy of nusinersen in individuals with more than two copies of SMN2 or symptom onset after 6 months of age. There are four additional ongoing clinical trials evaluating nusinersen's safety and efficacy in SMA, they include the following: (1) CHERISH, a Phase III study of type III SMA (late-onset) (NCT 02292537; ClinicalTrials.gov; expected completion: June 2017 ), (2 EMBRACE, ) a phase II randomized, double-blind, sham-procedure controlled study (NCT 02462759) for children diagnosed with SMA consistent with type II (intermediate disease severity) who were not eligible for enrollment in either ENDEAR or CHERISH, (3) an Expanded Access Program trial in infantile-onset SMA(NCT 02865109), and (4) SHINE, an open-label follow-up study of those enrolled in completed trials of nusinersen (NCT 02594124; clinicaltrials.gov).

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: 96450, J2326

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources


Senior Medical Director review 3/2017

Specialty Matched Consultant review 3/2017

Specialty Matched Consultant Advisory Panel 10/2017

Policy Implementation/Update Information

<table>
<thead>
<tr>
<th>Date</th>
<th>Description</th>
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<tbody>
<tr>
<td>3/31/17</td>
<td>New policy developed. Nusinersen may be considered medically necessary for the treatment of spinal muscle atrophy when criteria are met. (sk)</td>
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<td>6/30/17</td>
<td>Added J3590 and C9489 to Billing/Coding section for effective date 7/1/2017. (sk)</td>
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<td>12/29/17</td>
<td>Code J2326 added to Billing/Coding section for effective date 1/1/2018. Codes J3490, J3590, C9399, and C9489 deleted from Billing/Coding section effective 12/31/2017. (sk)</td>
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Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.