

Corporate Medical Policy

Nusinersen (Spinraza™)

File Name:	nusinersen_spinraza
Origination:	03/2017
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Description of Procedure or Service

Spinal muscular atrophy (SMA) is an inherited disorder caused by homozygous deletions or variants in the *SMN1* gene. As a consequence of low levels of SMN1 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 *SMN2* transcript causing the inclusion of exon 7 in the *SMN2* transcript, leading to production of full length functional SMN2 protein, which demonstrates similarity to SMN1.

SPINAL MUSCULAR ATROPHY

Spinal muscular atrophy (SMA) is a rare autosomal recessive genetic disorder caused by homozygous deletions or variants in the *SMN1* gene in chromosome 5. This gene is responsible for producing the “survival of motor neuron” protein (SMN1). As a consequence of absent or low levels of this 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. *SMN2* is a nearly identical modifying gene capable of producing compensatory SMN protein. However, 70% to 90% of the transcripts produced from the *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 *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. Only one copy of the *SMN2* gene is typically present.
- Type I (also called infantile SMA or Werdnig-Hoffman disease and subcategorized as IA, IB and IC): Onset is within 6 months of birth and symptoms progress rapidly, with most infants dying before 1 year of age from respiratory failure. About 60% of patients with SMA constitute of this phenotype. Two copies of the *SMN2* gene are present in approximately 85% of patients with type I SMA; the remainder have less than two copies.

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- Type II (also called intermediate SMA or Dubowitz disease): Onset is within 6 to 18 months with 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 independently. More than 70% of patients live beyond 25 years of age with adequate supportive care. Three copies of the *SMN2* gene are generally present.
- Type III (also called Kugelberg-Welander disease and subcategorized as IIIA and IIIB): Onset is 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. Three or four copies of the *SMN2* gene are typically present.
- Type IV (also called adult-onset SMA): Onset usually presents in the third decade of life and is otherwise similar to type III SMA. Patients remain ambulatory but may have hip and shoulder girdle weakness mimicking a mild limb-girdle muscular dystrophy. Four or more copies of the *SMN2* gene generally may be present.

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 exon 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 *SMN2* 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.

Related Policies:

Onasemnogene abeparvovec (Zolgensma®)

*****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.

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When Nusinersen (Spinraza™) is covered

Initial Therapy

Nusinersen is considered medically necessary for the treatment of spinal muscular atrophy (SMA) in individuals who meet **ALL** of the following criteria:

1. Documentation of a confirmed diagnosis of SMA by genetic testing (see Policy Guidelines); and
2. Documentation of two or more copies of the *SMN2* gene by genetic testing; and
3. SMA-associated symptom onset before 20 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) during the previous treatment period.

***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.

Concomitant use of nusinersen and onasemnogene abeparvovec (Zolgensma) is considered **investigational**.

Use of nusinersen after gene replacement therapy is considered **investigational**.

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. Genetic testing to confirm a diagnosis consists of homozygous deletion of *SMN1* exon 7 or compound heterozygosity for *SMN1* exon 7 deletion and small mutation.
3. 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 I (infantile-onset) SMA who receive nusinersen, the evidence includes 2 randomized, double-blind, controlled trial (results not yet reported for one) and a 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. The largest phase 3 confirmatory ENDEAR trial (N=121) showed

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clinically meaningful and statistically significant improvement in motor milestones, event-free survival, and overall survival that 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 51% in the nusinersen arm compared with 0% in the sham-controlled arm. Further, the hazard ratio for event-free survival was 0.53 favoring nusinersen over sham-controlled. It is notable, however, that 50% of nusinersen-treated subjects did not achieve the primary end point motor milestone response. Only a small proportion of patients (6%) gained the ability to sit without assistance. On average, mean motor milestone score in nusinersen-treated patients improved by 3 points over 6 months. 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 evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have type II or III SMA who receive nusinersen, the evidence includes 4 single-arm studies and a double-blind, randomized, controlled trial. 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. Efficacy findings from single-arm studies of type II and III SMA are difficult to interpret because these trials used a wide range of nusinersen doses and lacked control arms. The largest phase 3 confirmatory CHERISH trial (N=126) showed clinically meaningful and statistically significant improvement in motor milestones (measured using Hammersmith Functional Motor Scale-Expanded scores) that exceeded those seen in the control group (difference of 5.9 points favoring nusinersen over sham control, $p < 0.001$). The respective proportion of patients with clinically meaningful improvements in Hammersmith scores greater than 3 points was 57% versus 26% ($p < 0.001$). Multiple secondary endpoints also showed a consistency in treatment effect favoring nusinersen over sham control. Given the limited data on the durability of response, long-term safety, and lack of efficacy in a substantial number of patients, continued risk-benefit assessment of long-term treatment with nusinersen is necessary. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Although type III SMA is defined by the onset of SMA-related symptoms after age 18 months, the CHERISH trial included patients with symptom onset up to 20 months.

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

SPINRAZA (nusinersen) injection, for intrathecal use: Prescribing label. Biogen Inc. https://www.spinraza.com/content/dam/commercial/specialty/spinraza/caregiver/en_us/pdf/spinraza-prescribing-information.pdf. Accessed January 18, 2017.

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Chiriboga CA, Swoboda KJ, Darras BT, et al. Results from a phase 1 study of nusinersen (ISIS-SMN(Rx)) in children with spinal muscular atrophy. *Neurology*. Mar 08 2016;86(10):890-897. PMID 26865511

Senior Medical Director review 3/2017

Specialty Matched Consultant review 3/2017

Specialty Matched Consultant Advisory Panel 10/2017

BCBSA Medical Policy Reference Manual [Electronic Version]. 5.01.28, 4/12/2018

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Mercuri E, Darras BT, Chiriboga CA, et al. Nusinersin versus sham control in later-onset spinal muscular atrophy. *N Engl J Med*. 2018;378:625-35.

Butchbach ME. Copy number variations in the survival motor neuron genes: implications for spinal muscular atrophy and other neurodegenerative diseases. *Front Mol Biosci*. 2016;3:7. Available at: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4785180/>. Accessed May 2018.

Kolb SJ, Kissel JT. Spinal muscular atrophy. *Neurol Clin*. 2015;33(4):831. Available at: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4628728/pdf/nihms707577.pdf>. Accessed May 2018.

Medical Director review 6/2018

Specialty Matched Consultant Advisory Panel 10/2018

Medical Director review 11/2018

Medical Director review 6/2019

Policy Implementation/Update Information

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| 3/31/17 | New policy developed. Nusinersen may be considered medically necessary for the treatment of spinal muscle atrophy when criteria are met. (sk) |
| 6/30/17 | Added J3590 and C9489 to Billing/Coding section for effective date 7/1/2017. (sk) |
| 11/10/17 | Specialty Matched Consultant Advisory Panel review 10/25/2017. (sk) |
| 12/29/17 | 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) |
| 6/29/18 | Updated “When Covered” section to include the following initial therapy criteria: “genetic testing confirming two or more copies of the SMN2 gene, and SMA-associated symptom onset before 20 months of age.” Updated wording of criterion A in “When Covered” section to provide more clarity with no change to intent. Additions made to Description section to include number of copies of SMN2 gene per SMA type for clarity. Updated Policy Guidelines section with additional clinical trial data. References added. Medical Director review 6/2018. (krc) |

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- 11/9/18 Specialty Matched Consultant Advisory Panel review 10/24/2018. (krc)
- 11/30/18 Updated formatting of “When Covered” section to provide additional clarity and moved statements “homozygous deletion of SMN1 exon 7 or compound heterozygosity for SMN1 exon 7 deletion and small mutation” to Policy Guidelines section. No change to policy intent. Added clarification regarding SMN2 gene copies to definition of type I SMA in Description section. Added trial data to include age of study participants in CHERISH trial for clarity. Minor typographical edits made. Medical Director review 11/2018. (krc)
- 6/11/19 Added the following statements to “When Not Covered” section: “Concomitant use of nusinersen and onasemnogene abeparvovec (Zolgensma) is considered investigational,” and “Use of nusinersen after gene replacement therapy is considered investigational.” Added reference to ‘Onasemnogene abeparvovec (Zolgensma®)’ as a related policy. Medical Director review 6/2019. (krc)

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.