

## Medical Coverage Policy | Nusinersen For Spinal Muscular Atrophy



**EFFECTIVE DATE:** 03|07|2017

**POLICY LAST UPDATED:** 03|07|2017

### OVERVIEW

Spinal muscular atrophy (SMA) is an inherited disorder caused by homozygous deletions or variants in the *SMN1* gene. As a consequence of absent or 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 is very similar to SMN1.

### MEDICAL CRITERIA

#### BlueCHiP for Medicare and Commercial

Nusinersen may be considered **medically necessary** for patients with infantile-onset or type I spinal muscular atrophy with a documented genetic diagnosis of spinal muscular atrophy.

### PRIOR AUTHORIZATION

Prior authorization is required for BlueCHiP for Medicare and recommended for Commercial Products

### POLICY STATEMENT

Nusinersen may be considered **medically necessary** for patients with infantile-onset or type I spinal muscular atrophy with a documented genetic diagnosis of spinal muscular atrophy.

**Note:** The recommended dosage is 12 mg (5 mL) administered intrathecally. Treatment is initiated with 4 loading doses; the first 3 loading doses should be administered at 14-day intervals while the fourth loading dose is administered 30 days after the third loading dose. Subsequent maintenance doses should be administered once every 4 months thereafter.

Nusinersen is considered not medically for patients with type 0, II, III, and IV spinal muscular atrophy as the evidence is insufficient to determine the effects of the technology on health outcomes.

**Authorization period will be for 1 year.**

### COVERAGE

Benefits may vary between groups and contracts. Please refer to the appropriate Benefit Booklet, Evidence of Coverage or Subscriber Agreement for applicable not medically necessary services.

### BACKGROUND

#### 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 SMN1, 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 nearly identical compensatory SMN2 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. 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 for 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. 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. 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 and is otherwise similar to SMA type III.

### **Infantile-Onset or Type I SMA**

For individuals who have type I (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 presymptomatic infantile-onset SMA patients found a benefit of early treatment with nusinersen. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

### **Type II and III SMA**

For individuals who have type I or II SMA who receive nusinersen, the evidence includes 4 single-arm studies and 1 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. Results of the confirmatory phase 3 CHERISH trial are not yet available. The evidence is insufficient to determine the effects of the technology on health outcomes.

### **Type 0 or IV SMA**

For individuals who have type 0 SMA or type IV SMA who receive nusinersen, no studies were identified. Relevant outcomes are change in disease status, morbid events, functional outcomes, health status measures,

quality of life, and treatment-related mortality and morbidity. The evidence is insufficient to determine the effects of technology on health outcomes

### Regulatory Status

In 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.

### CODING

There is no specific HCPCS code at this time, claims must be filed with an unlisted code such as J3490 and the NDC number

### RELATED POLICIES

none

### PUBLISHED

Provider Update May 2017

### REFERENCES:

1. Wang CH, Finkel RS, Bertini ES, et al. Consensus statement for standard of care in spinal muscular atrophy. *J Child Neurol.* Aug 2007;22(8):1027-1049. PMID 17761659
2. Lorson CL, Hahnen E, Androphy EJ, et al. A single nucleotide in the SMN gene regulates splicing and is responsible for spinal muscular atrophy. *Proc Natl Acad Sci U S A.* May 25 1999;96(11):6307-6311. PMID 10339583
3. Lefebvre S, Burlet P, Liu Q, et al. Correlation between severity and SMN protein level in spinal muscular atrophy. *Nat Genet.* Jul 1997;16(3):265-269. PMID 9207792
4. Muscular Dystrophy Association. Spinal Muscular Atrophy. n.d.; <https://www.mda.org/disease/spinal-muscular-atrophy>. Accessed January 18, 2017.
5. National Organization for Rare Disorders, Russman B. Spinal Muscular Atrophy. 2012; <https://rarediseases.org/rare-diseases/spinal-muscular-atrophy/>. Accessed January 18, 2017.
6. Zerres K, Rudnik-Schoneborn S. Natural history in proximal spinal muscular atrophy. Clinical analysis of 445 patients and suggestions for a modification of existing classifications. *Arch Neurol.* May 1995;52(5):518-523. PMID 7733848
7. Finkel RS, McDermott MP, Kaufmann P, et al. Observational study of spinal muscular atrophy type I and implications for clinical trials. *Neurology.* Aug 26 2014;83(9):810-817. PMID 25080519
8. Rudnik-Schoneborn S, Hausmanowa-Petrusewicz I, Borkowska J, et al. The predictive value of achieved motor milestones assessed in 441 patients with infantile spinal muscular atrophy types II and III. *Eur Neurol.* 2001;45(3):174-181. PMID 11306862
9. Prior TW. Perspectives and diagnostic considerations in spinal muscular atrophy. *Genet Med.* Mar 2010;12(3):145-152. PMID 20057317
10. Sugarman EA, Nagan N, Zhu H, et al. Pan-ethnic carrier screening and prenatal diagnosis for spinal muscular atrophy: clinical laboratory analysis of >72,400 specimens. *Eur J Hum Genet.* Jan 2012;20(1):27-32. PMID 21811307
11. Prior TW, Snyder PJ, Rink BD, et al. Newborn and carrier screening for spinal muscular atrophy. *Am J Med Genet A.* Jul 2010;152A(7):1608-1616. PMID 20578137
12. 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](https://www.spinraza.com/content/dam/commercial/specialty/spinraza/caregiver/en_us/pdf/spinraza-prescribing-information.pdf). Accessed January 18, 2017.
13. Finkel RS, Chiriboga CA, Vajsar J, et al. Treatment of infantile-onset spinal muscular atrophy with nusinersen: a phase 2, open-label, dose-escalation study. *Lancet.* Dec 17 2017;388(10063):3017-3026. PMID 27939059

14. Biogen, RTI Helath Solutions. Formulary Submission Dossier: Spinraza (Nusinersen) for Spinal Muscular Atrophy (NS-US-0199). Cambridge, MA 2016 December.
15. Finkel RS, Kuntz N, Mercuri E, et al. Primary Efficacy and Safety Results From the Phase 3 ENDEAR Study of Nusinersen in Infants Diagnosed With Spinal Muscular Atrophy (SMA). Paper presented at: 43rd Annual Congress of the British Paediatric Neurology Association; January 11-13 2017; Cambridge, UK.
16. 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
17. National Institute for Health and Care Excellence. Proposed technology appraisals: Nusinersen for treating spinal muscular atrophy. n.d.; <https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-technology-appraisal-guidance/proposed-technology-appraisals#Nusinersen>. Accessed January 20, 2017.

**CLICK THE ENVELOPE ICON BELOW TO SUBMIT COMMENTS**

This medical policy is made available to you for informational purposes only. It is not a guarantee of payment or a substitute for your medical judgment in the treatment of your patients. Benefits and eligibility are determined by the member's subscriber agreement or member certificate and/or the employer agreement, and those documents will supersede the provisions of this medical policy. For information on member-specific benefits, call the provider call center. If you provide services to a member which are determined to not be medically necessary (or in some cases medically necessary services which are non-covered benefits), you may not charge the member for the services unless you have informed the member and they have agreed in writing in advance to continue with the treatment at their own expense. Please refer to your participation agreement(s) for the applicable provisions. This policy is current at the time of publication; however, medical practices, technology, and knowledge are constantly changing. BCBSRI reserves the right to review and revise this policy for any reason and at any time, with or without notice. Blue Cross & Blue Shield of Rhode Island is an independent licensee of the Blue Cross and Blue Shield Association.

