

---

**Subject:** Nusinersen (SPINRAZA™)

**Policy #:** DRUG.00104

**Current Effective Date:** 05/18/2017

**Status:** Revised

**Last Review Date:** 05/04/2017

---

### Description/Scope

This document addresses the uses of nusinersen (SPINRAZA, Biogen Inc., Cambridge, MA) in the treatment of spinal muscular atrophy (SMA). Nusinersen is an intrathecally administered antisense oligonucleotide that increases the amount of functional survival motor neuron (SMN) protein which is deficient in individuals diagnosed with SMA. SMA is a rare, and often fatal, genetic disease affecting muscle strength and movement.

---

### Position Statement

#### Medically Necessary:

##### *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:
    - 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. Onset of SMA-associated signs and symptoms before 21 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 signs and 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.

### **Investigational and Not Medically Necessary:**

Use of nusinersen is considered **investigational and not medically necessary** when the criteria above are not met and for all other indications, including but not limited to non-5q-spinal muscular atrophy disorders.

|                  |
|------------------|
| <b>Rationale</b> |
|------------------|

On December 23, 2016 nusinersen was granted accelerated approval by the U.S. Food and Drug Administration (FDA) for the treatment of SMA. The FDA granted nusinersen fast-track, priority review and orphan drug designation (Product Information [PI] Label, 2016). Nusinersen is the first drug approved to treat children and adults with SMA, a rare and often fatal genetic disease affecting muscle strength and movement. Nusinersen is an antisense oligonucleotide, a drug class that does not cross the blood-brain barrier and as a result, it must be administered by intrathecal injection.

Nusinersen's approval was based on positive interim results of an unpublished Phase III, double-blind, controlled clinical trial, known as ENDEAR, conducted in infants, aged 7 months or younger at study entry, who were diagnosed with symptomatic infantile-onset SMA (Type I). Inclusion criteria specified confirmatory diagnosis of SMA consistent with type I severity had been determined by identification of two copies of SMN2 (see Background/Overview for more information), age of onset (symptom onset before 6 months of age), and symptom severity. A total of 82, out of 121 infants enrolled in ENDEAR (NCT 02193074), were included in the interim analysis. Study participants were enrolled 2:1 and all infants included in the interim analysis had died, withdrawn or completed at least 183 days (6 months) of treatment. Baseline disease characteristics were similar between study arms with the exception of the nusinersen-treatment group having a higher percentage of paradoxical breathing, pneumonia, respiratory symptoms, swallowing/feeding difficulty and need for respiratory support. Also, 88% of the treatment group and only 77% of the control group, experienced symptoms within the first 3 months of life. Demographics were well balanced with the exception of the treatment group being an average of 31 days younger than the control group at the start of treatment (median age 175 vs. 206 days, respectively). Despite the treatment group

having more severe symptoms at baseline, the trial found 40% of those treated, compared with 0% of those in the control arm, demonstrated improvement in motor milestones such as head control, sitting, crawling and standing ( $p < 0.0001$ ). Furthermore, as assessed by the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND), 63% ( $n=33$ ) of infants treated with nusinersen improved by at least 4 points, whereas only 3% ( $n=1$ ) achieved this improvement in the control arm. Similarly, 40% ( $n=12$ ) of the control arm worsened by at least 4 points on the CHOP-INTEND test whereas only 4% ( $n=2$ ) of the treatment arms experienced this decline in motor function. The most common adverse events that occurred in the treatment arm more often than the control arm were respiratory infections and constipation. Atelectasis, a serious adverse reaction, was more frequent in the treatment arm (14%) compared to the control arm (5%) (FDA PI Label, 2016). This clinical trial is now open-label and is ongoing.

Finkel and colleagues (2016) published nusinersen safety and efficacy data from a phase II open-label, dose-escalation study which enrolled 20 infants who were between 3 weeks and 7 months of age and had SMN1 homozygous gene deletion or mutation with onset of SMA symptoms between 3 weeks and 6 months of age (SMA type I); 17/20 participants had two copies of SMN2. Outcomes included several measures of safety as well as event free survival, change in the motor milestones portion of the Hammersmith Infant Neurological Exam-Part 2 (HINE-2) and the CHOP-INTEND motor function test. Time to death or permanent ventilation was compared with natural history data of infants with SMA (Finkel, 2014). At the time of the interim analysis the publication was based on, the 6-12 mg group ( $n=4$ ; 6 mg loading doses administered on days 1, 15 and 85 and 12 mg doses on day 253 and every 4 months thereafter) had been followed for 9-32 months and received four to nine doses of nusinersen, whereas the 12 mg group ( $n=16$ ; 12 mg doses administered on the same schedule as the 6-12 mg group) had been followed for 2-27 months and received two to eight doses. Although all study participants experienced adverse events, none were determined to have likely been related to nusinersen administration. The most common adverse events were respiratory-related which are frequent in infants with SMA. In the 12 mg dose group, incremental achievements of motor milestones ( $p < 0.0001$ ) and improvements in CHOP-INTEND motor function scores ( $p = 0.0013$ ) from baseline were reported. The median age at death or permanent ventilation was not reached and the Kaplan-Meier survival curve diverged significantly from a published natural history case series ( $p = 0.0014$ ). The results of this trial informed the design of the Phase III clinical study on which nusinersen's approval was based.

A Phase I nusinersen dose-finding study (1, 3, 6 and 9 mg) in SMA types II and III enrolled 28 children aged 2-14 years (Chiriboga, 2016); 25/28 participants had 3 copies of SMN2. There were no safety or tolerability issues identified in this older cohort of children with SMA types II and III and a significant increase in the exploratory endpoint of Hammersmith Functional Motor Scale Expanded (HFMSSE) scores was seen at the 9-mg dose (+3.1 points;  $p = 0.016$ ). Authors concluded that the risk-benefit profile was favorable for further investigation of nusinersen's safety and efficacy in this population.

In 2017, Mercuri and colleagues presented the results of a Phase III, multicenter, randomized, double-blind, sham procedure-controlled study conducted in children with later-onset SMA at the American Academy of Neurology (AAN) Annual Meeting (NCT 02292537; ClinicalTrials.gov). Children with symptomatic SMA aged 2 to 12 years were enrolled and randomized 2:1 to receive 4 doses of nusinersen (12 mg dose; n=84) or a sham procedure control (n=42) during the 15-month study. The study inclusion criteria included confirmed diagnosis of 5q SMA, onset of clinical symptoms after 6 months of age and the ability to sit independently but never attained the ability to walk independently. Of the children enrolled, 100% had symptom onset by 21 months of age. The primary outcome was an improvement from baseline in HFMSE. At study-end, the change from baseline in HFMSE score was significantly different in the nusinersen arm versus the control arm (4.9 point difference;  $p < 0.000$ ), with a mean improvement of 3.9 points in the nusinersen arm and a mean 1.0-point decline in the control arm. There were no treatment-related discontinuations related to adverse events and no new safety concerns emerged.

Package labeling noted that unpublished data from additional open-label, non-controlled trials support the safety and efficacy of nusinersen in both pre-symptomatic and symptomatic SMA disease presentation. The open-label clinical studies included symptomatic SMA study participants aged 30 days to 15 years old at the time of enrollment and pre-symptomatic participants ranging in age from 8 days to 42 days at enrollment. Nusinersen was determined to illicit an immunogenic response in 126 of the 173 individuals exposed to the drug in clinical trials who had baseline plasma samples evaluated for anti-drug antibodies (ADAs). At this time, the FDA has stated, "There are insufficient data to evaluate an effect of ADAs on clinical response, adverse events, or the pharmacokinetic profile of nusinersen" (FDA PI Label, 2016).

There are three additional ongoing clinical trials evaluating nusinersen's safety and efficacy in SMA, they include the following: (1) a phase II randomized, double-blind, sham-procedure controlled study known as EMBRACE (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, (2) an Expanded Access Program trial in infantile-onset SMA (NCT 02865109), and (3) an open-label follow-up study of those enrolled in completed trials of nusinersen, known as SHINE (NCT 02594124; clinicaltrials.gov).

## **Background/Overview**

### *Spinal Muscular Atrophy (SMA)*

SMA is largely an inherited autosomal recessive disease caused by mutations in chromosome 5q that lead to a deficiency in SMN1-related proteins. In rare instances (2-3% of SMA), SMA can occur de novo, where a mutation occurs in an individual during egg or sperm production, rather than inheriting a defective copy of the gene from each parent. This deficiency results in degeneration of motor neurons causing muscle atrophy, particularly in the limbs and the muscles that control the mouth, throat and

respiration. There are four types of SMA, types I, II, III, and IV which are defined based on the severity of muscle weakness and the age of symptom onset. SMA type I (Werdnig-Hoffmann disease) is the most severe. SMA type I-affected infants represent approximately 60% of SMA diagnoses and present with the disease by 6 months of age. These infants are profoundly hypotonic and often succumb to complications of the disease by their second year of life. SMA type II affected children (intermediate form) present with symptoms prior to 18 months of age and develop the ability to sit unaided but not the ability to stand or walk. Individuals affected by SMA type III (Kugelberg-Welander disease) are also generally diagnosed by 18 months but are able to stand and walk. SMA type III affected individuals may live into their thirties and beyond. SMA IV, the least severe, typically presents in the second or third decade of life, but is otherwise similar to type III.

SMN2, a closely related gene to SMN1 that also produces functional SMN, can compensate for SMN1 deficiency and modify the SMA phenotype. Therefore, although the role of SMN protein in motor neurons is not completely understood and the amount for normal functioning undefined, the phenotype of spinal muscular atrophy (type I, II, III, or IV) is largely related to the number of SMN2 gene copies present. The number of copies of SMN2 in individuals diagnosed with SMA has been found to negatively correlate with disease severity. For instance, infants diagnosed with SMA type I, are likely to have two copies or less of SMN2 and individuals with SMA type III and IV are likely to have three copies or more (Mailman, 2002).

A number of other motor neuron diseases exist, also termed SMA, that are caused by mutations in genes other than the SMN1 gene. These are referred to as non-5q- SMA diseases, meaning that the genes causing these forms of SMA are not located in the SMN region of chromosome 5.

The incidence of SMA is approximately 1 in 10,000 live births with an estimated carrier frequency of 1 in 50. Standard of care for SMA has historically been based on supportive therapy which includes nutrition, physical therapy, and respiratory assistance. SMA is the leading genetic cause of death in infants, but can affect individuals at any stage of life.

Nusinersen is an antisense oligonucleotide designed to treat SMA by altering SMN2 promoting increased production of functional SMN. Nusinersen is the first drug to receive FDA approval for the treatment of children and adults with SMA.

### *Adverse Events and Warnings*

Warnings and recommendations from the FDA PI Label (2016) include:

- *Thrombocytopenia and Coagulation Abnormalities:* Increased risk for bleeding complications; platelet count and coagulation laboratory testing required at baseline and before each dose of nusinersen.

- *Renal Toxicity*: Quantitative spot urine protein testing required at baseline and prior to each dose of nusinersen.
- The most common adverse reactions to nusinersen were lower respiratory infection, upper respiratory infection, and constipation.

## Definitions

Antisense oligonucleotide: Synthetic single stranded nucleic acids that bind to RNA and thereby alter or reduce expression of the target RNA.

Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders: A test developed to evaluate the motor skills of infants with SMA type I.

Hammersmith Functional Motor Scale Expanded: A validated functional motor scale devised for use in children SMA type II and type III to give objective information on motor ability and clinical progression.

Hammersmith Infant Neurological Exam: A widely used method for assessing neuromotor development in infants between 2 and 24 months of age.

Non-5q- spinal muscular atrophy diseases: Forms of SMA caused by genes that are not located in the SMN region of chromosome 5.

## Coding

*The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.*

### When services may be Medically Necessary when criteria are met:

#### CPT

96450 Chemotherapy administration, into CNS (eg, intrathecal), requiring and including spinal puncture [when associated with administration of nusinersen (SPINRAZA)]

#### HCPCS

J3490 Unclassified drugs [when specified as nusinersen (SPINRAZA)]

#### ICD-10 Diagnosis

G12.0 Infantile spinal muscular atrophy, type I (Werdnig-Hoffman)  
 G12.1 Other inherited spinal muscular atrophy [includes types II, III (Kugelberg-Welander) and IV]

### **When services are Investigational and Not Medically Necessary:**

For the procedure and diagnosis codes listed above when criteria are not met or for all other diagnoses not listed; or when the code describes a procedure indicated in the Position Statement section as investigational and not medically necessary.

## **References**

### **Peer Reviewed Publications:**

1. 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*. 2016; 86(10):890-897.
2. 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*. 2016; 388(10063):3017-3026.
3. Finkel RS, McDermott MP, Kaufmann P, et al. Observational study of spinal muscular atrophy type I and implications for clinical trials. *Neurology*. 2014; 83(9):810-817.
4. Mailman M, Heinz J, Papp A, et al. Molecular analysis of spinal muscular atrophy and modification of the phenotype by SMN2. *Genet Med*. 2002; 4(1):20-26.
5. Mercuri E, Finkel J, Kirschner J, et al. Efficacy and safety of nusinersen in children with later-onset spinal muscular atrophy (SMA): results of the phase 3 CHERISH study. American Academy of Neurology (AAN) Annual Meeting Abstract. Available at: <https://www.aan.com/conferences/2017-annual-meeting/abstracts/>. Accessed on May 09, 2017.

### **Government Agency, Medical Society, and Other Authoritative Publications:**

1. Biogen Inc. A study of multiple doses of nusinersen (ISIS 396443) delivered to infants with genetically diagnosed and presymptomatic spinal muscular atrophy (NURTURE). NLM Identifier: NCT02386553. Available at: <https://clinicaltrials.gov/ct2/show/NCT02386553?term=nurture+sma&rank=1>. Accessed on April 07, 2017.
2. Biogen Inc. A study to assess the efficacy and safety of IONIS-SMN Rx in patients with later-onset spinal muscular atrophy (CHERISH). NLM Identifier: NCT02292537. Available at: <https://clinicaltrials.gov/ct2/show/NCT02292537?term=NCT02292537&rank=1>. Accessed on April 07, 2017.
3. Biogen Inc. A study to assess the safety and tolerability of nusinersen (ISIS 396443) in participants with spinal muscular atrophy (SMA). (EMBRACE). NLM Identifier: NCT02462759. Available at: <https://clinicaltrials.gov/ct2/show/NCT02462759?term=EMBRACE++sma&rank=1>. Accessed on April 07, 2017.
4. Biogen Inc. An open-label study (SHINE) for patients with spinal muscular atrophy (SMA) who participated in Studies with IONIS-SMNRx. NLM Identifier: NCTNCT02594124. Available

at: <https://clinicaltrials.gov/ct2/show/NCT02594124?term=shine+sma&rank=1>. Accessed on April 07, 2017.

5. Biogen Inc. Expanded Access Program (EAP) for nusinersen in participants with infantile-onset (consistent with type 1) spinal muscular atrophy (SMA). NLM Identifier: NCT02865109. Available at: <https://clinicaltrials.gov/ct2/show/NCT02865109?term=nusinersen&rank=2>. Accessed on April 07, 2017.
6. SPINRAZA (nusinersen) [Product Information Label]. Cambridge, MA. Biogen Inc. December 2016. Available at [http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2016/209531lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/209531lbl.pdf). Accessed on April 07, 2016.

### Websites for Additional Information

1. Cure SMA. The genetics of spinal muscular atrophy. 2009. Available at: <http://www.curesma.org/documents/support--care-documents/genetics-of-sma.pdf>. Accessed on April 07, 2017.
2. Genetics Home Reference. Spinal muscular atrophy. Available at <https://ghr.nlm.nih.gov/condition/spinal-muscular-atrophy>. Accessed on April 07, 2016.

### Index

**The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.**

### Document History

| Status  | Date       | Action  |
|---------|------------|---|
| Revised | 05/04/2017 | Medical Policy & Technology Assessment Committee (MPTAC) review. Clarified criteria and expanded age of symptom onset to before 21 months of age. Updated References and Websites sections. |
| Revised | 02/02/2017 | MPTAC review. Added a "Note" to the MN Criteria for clarification of Continuation intent.   |
| New     | 01/18/2017 | MPTAC review. Initial document development.   |

---

Applicable to Commercial HMO members in California: When a medical policy states a procedure or treatment is investigational, PMGs should not approve or deny the

request. Instead, please fax the request to Anthem Blue Cross Grievance and Appeals at fax # 818-234-2767 or 818-234-3824. For questions, call G&A at 1-800-365-0609 and ask to speak with the Investigational Review Nurse.

Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Medical Policy, which addresses medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.

© CPT Only – American Medical Association