Cigna Drug and Biologic Coverage Policy

Effective Date **5/15/2017**
Next Review Date **5/15/2018**
Coverage Policy Number **1707**

Subject **Nusinersen**

Table of Contents

Related Coverage Resources

Genetic Testing for Hereditary and Multifactorial Conditions

INSTRUCTIONS FOR USE

*The following Coverage Policy applies to health benefit plans administered by Cigna companies. Coverage Policies are intended to provide guidance in interpreting certain **standard** Cigna benefit plans. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document **always supersedes** the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations. Proprietary information of Cigna. Copyright ©2017 Cigna*

Coverage Policy

Cigna covers nusinersen (Spinraza™) as medically necessary for the treatment of spinal muscular atrophy (SMA) when all of the following criteria are met:

- Documented diagnosis of Type 1 SMA supported by clinical records
- Onset of clinical signs and symptoms consistent with SMA at age 6 months or younger
- At least two (2) copies of Survival Motor Neuron 2 (SMN2)
- Genetic documentation of SMN1, SMA, or 5q SMA homozygous gene deletion, homozygous mutation, or compound heterozygote mutation

Initial authorization for 6 months. Reauthorization requires meeting initial criteria AND documentation of a positive clinical response (for example: improvement or stabilization of motor milestones) from pretreatment baseline status with nusinersen (Spinraza) therapy.

Cigna does not cover the use of nusinersen (Spinraza) for any other indication including the following because it is considered experimental, investigational or unproven (this list may not be all-inclusive):

- Types 0, 2, 3, or 4 SMA

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to nusinersen (Spinraza).

Note: Receipt of sample product does not satisfy any criteria requirements for coverage.

FDA Approved Indication
Spinraza is indicated for the treatment of spinal muscular atrophy (SMA) in pediatric and adult patients.

FDA Recommended Dosing
Spinraza is administered intrathecally by, or under the direction of, healthcare professionals experienced in performing lumbar punctures.

Recommended Dosage
The recommended dosage is 12 mg (5 mL) per administration.

Initiate Spinraza treatment with 4 loading doses. The first three loading doses should be administered at 14-day intervals. The 4th loading dose should be administered 30 days after the 3rd dose. A maintenance dose should be administered once every 4 months thereafter.

Missed Dose
If a loading dose is delayed or missed, administer Spinraza as soon as possible, with at least 14-days between doses and continue dosing as prescribed. If a maintenance dose is delayed or missed, administer Spinraza as soon as possible and continue dosing every 4 months.

Drug Availability
Spinraza injection is a sterile, clear and colorless solution supplied as a 12 mg/5 mL (2.4 mg/mL) solution in a single-dose glass vial free of preservatives.

General Background
Disease Overview
Spinal muscular atrophy is a hereditary neuromuscular disorder affecting 8 to 15 in 100,000 live births. (Darras, 2015; Sarnat, 2016) Symptom onset typically occurs in infancy or childhood, and the disease is characterized by progressive muscle weakness ultimately resulting in respiratory failure and death in severe cases. (Tisdale, 2015) Spinal muscular atrophy is classified into 1 of 5 categories (i.e., Type 0 through Type 4) based mainly on age at symptom onset and severity of symptoms, which are widely variable. (Arnold, 2015; Darras, 2015; Tisdale, 2015) Type 1 SMA is the most common form, occurs in infancy, and patients typically do not survive past 2 years of age without respiratory support. Type 4 SMA is the mildest form, characterized by mild proximal muscle weakness starting in adulthood, and does not reduce life expectancy. Patients with clinical symptoms suggestive of SMA undergo genetic testing to confirm the diagnosis. (Arnold, 2015; Darras, 2015; Tisdale, 2015) Table 1 summarizes the characteristics of each type of SMA.

Table 1. Types of Spinal Muscular Atrophy[a]

SMA Type (Proportion)	Age at Onset	Clinical Presentation	Typical Number of *SMN2* Copies	Life Expectancy[b]
Type 0 (< 1%)	Prenatal to birth	• Areflexia • Atrial septal defect • Facial diplegia • Hypotonia • Joint contracture • Poor feeding • Reduced fetal movement • Respiratory failure (often at birth) • Severe weakness • Weak cry	1 copy	< 6 mo
Type 1 Werdnig-Hoffman disease	Birth to 6 mo	• Never able to sit unassisted • Areflexia or hyporeflexia • Dysphagia	2 to 3 copies	< 2 y

SMA Type (Proportion)	Age at Onset	Clinical Presentation	Typical Number of *SMN2* Copies	Life Expectancy[b]
(25% to 60%)		• Hypotonia • Intercostal muscle weakness • Joint contractures • Lack of head control • Muscle atrophy • Progressive muscle weakness • Poor feeding • Respiratory distress in first year of life • Tongue fasciculations and weakness • Weak cry		
Type 2 Dobowitz disease (20% to 50%)	6 to 18 mo	• Able to sit unassisted • Never able to stand or walk unassisted • Areflexia or hyporeflexia • Aspiration and respiratory distress • Dysphagia • Hypotonia • Intercostal muscle weakness • Joint contractures • Progressive muscle weakness • Scoliosis • Restrictive lung disease • Tremor (minipolymyoclonus) • Tongue fasciculations and atrophy	3 copies	School age to young adult
Type 3 Kugelberg-Welander disease (12% to 30%)	18 mo to adulthood	• Able to walk unassisted, but may eventually require wheelchair • Fasiculations • Muscle hypertrophy (not atrophy) • Progressive proximal weakness • Respiratory muscle weakness is minimal • Severe scoliosis not likely • Tremor (minipolymyoclonus)	3 to 4 copies	Normal
Type 4 (< 5%)	> 21 y	• Able to reach all motor milestones • Mild proximal muscle weakness • Initial symptoms similar to Type 3, but later onset and less severe	≥ 4 copies	Normal

[a] Data derived from Arnold, 2015; Darras, 2015; Kolb, 2015; Sarnat, 2016; and Tisdale, 2015.
[b] Without respiratory support
Abbreviations: SMA = spinal muscular atrophy; SMN = survival motor neuron

- **Genetic Testing**

Most forms of SMA are due to an autosomal recessive homozygous mutation or deletion at the 5q13 position of the survival motor neuron 1 gene (SMN1). (Kolb, 2015) Approximately 1 in 50 people are carriers for the abnormal SMN1 gene. (Arnold, 2015; Tisdale, 2015) The SMN1 gene produces SMN protein which is required for RNA splicing and is present in cells throughout the human body. (Arnold, 2015) Motor neurons normally have higher expression of SMN protein than other cells and are thought to require more SMN in order to function normally. (Arnold, 2015) Patients with SMA are unable to produce adequate levels of SMN protein, resulting in motor neuron degeneration and progressive muscle weakness and atrophy. (Arnold, 2015; Darras, 2015; Tisdale, 2015) The SMN2 gene has an identical amino acid sequence to SMN1 other than a C to T transition in exon 7, and is not affected in patients with SMA. The C to T transition results in exon 7 being

spliced out of mRNA transcription from SMN2, and formation of mostly truncated and unstable SMN protein. The SMN2 gene produces a small amount of functional SMN protein. The number of copies of the SMN2 gene is variable in humans. In SMA, a higher number of SMN2 copies is correlated with less severe disease. (Arnold, 2015; Darras, 2015; Tisdale, 2015)

Pharmacology
Nusinersen is an antisense oligonucleotide that increases the amount of functional SMN protein produced by the SMN2 gene. Nusinersen binds to the ISS-N1 intron to suppress splicing of exon 7 in SMN2. Increased inclusion of exon 7 in SMN2 mRNA transcripts increases production of functional SMN protein. (Rigo, 2014)

Guidelines
The most recent SMA treatment recommendations were published in 2012 by the French Association to Fight Myopathies, prior to approval of nusinersen, and its place in therapy is not addressed. There is no cure for SMA. The treatment recommendations are focused on supportive care for management of joint contractures, scoliosis, swallowing difficulties, and malnutrition. (Cuisset, 2012)

Clinical Efficacy
There are no published randomized, controlled trials evaluating nusinersen. In infants with SMA, nusinersen improved motor function compared with sham IT procedure in an unpublished, randomized, controlled trial, and improved motor function and ventilator-free survival in a small, open-label published study.

Several different scales were used to assess motor function and efficacy of nusinersen in clinical trials and are summarized in Table 2.

Table 2. Outcomes Used in Clinical Trials Evaluating Nusinersen Efficacy for SMA

Outcome	Description
Hammersmith Infant Neurological Exam Section 2 (HINE-2)	• Clinician-administered tool to evaluate motor function in children age 2 to 24 mo • Measures achievement of 26 motor milestones in 8 areas (ie, walking, standing, crawling, rolling, kicking, grasping, sitting, and head control) • Higher scores indicate better function
Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND)	• Clinician-administered tool designed to evaluate motor function in infants with SMA • Includes 16 items • Total scores range from 0 to 64 points • Higher scores indicate better function
Hammersmith Functional Motor Scale-Expanded (HFMSE)*	• Clinician-administered tool designed to measure motor function in children with SMA Type 2 and 3, including ambulatory SMA Type 3 patients • Includes 33 items, each scored from 0 (unable to perform activity) to 2 (able to perform activity without assistance or modification) • Total scores range from 0 to 66 points • Higher scores indicate better function • 3-point change is considered clinically significant

*Glanzman, 2011; Mazzone, 2015

The unpublished ENDEAR study randomized 121 infants with SMA to nusinersen 12 mg IT or a sham IT procedure. (CDER, 2016b) Infants were eligible if they had genetic documentation of 5q SMA homozygous gene deletion, homozygous mutation, or compound heterozygote; onset of clinical signs and symptoms consistent with SMA at 6 months of age or younger; and SMN2 copy number equaled 2. (CDER, 2016a) An interim efficacy analysis was conducted with a data cutoff date of June 15, 2016 in patients who completed their visit in study day 183. The primary outcomes were time to death or permanent ventilation (evaluated in intention-to-treat set), and the proportion of motor milestone responders (evaluated in the interim analysis set). Permanent ventilation was defined as either receipt of a tracheostomy, or ventilatory support required for 16 or more hours per day for 21 or more days in a row. Motor milestone responders were defined as those who had more HINE-2 category scores that were improved from baseline than worsened, and achieved either an increase of 2 or more points or the maximum HINE-2 score for ability to kick, or an increase of 1 or more points in the HINE-2 score for walking, standing, crawling, sitting, rolling, or head control. Patients who died or withdrew from the study were counted as nonresponders. More patients in the nusinersen group were

considered motor milestone responders (41%) compared with sham IT procedure (0%, P < 0.0001). Results were consistent across individual HINE-2 category scores and in sensitivity analyses that used slightly different response definitions and methods for accounting for missing data. The time to death or permanent ventilation was not reported. (CDER, 2016b) Nusinersen IT injection was well-tolerated, and no treatment-related adverse events occurred. (Kuntz, 2016)

An open-label, sequential-dosing study in 20 infants with SMA symptom onset between 3 and 22 weeks of age was conducted. Motor function and ventilator-free survival in nusinersen-treated patients were compared with historical controls. All patients were between 5 and 30 weeks of age at the time of study enrollment and had homozygous SMN1 deletion or mutation. Most patients (85%) had 2 SMN2 copies, 10% had 3 SMN2 copies, and the number of SMN2 copies was unknown in 1 patient. Nusinersen was administered by IT injection on study days 1, 15, 85, 253, and every 4 months thereafter. The first 4 patients enrolled in the study received nusinersen 6 mg for the first 3 doses and received 12 mg thereafter. The remaining 16 patients received nusinersen 12 mg throughout the study. An interim efficacy analysis was conducted approximately 18 months after the final patient was enrolled in 19 patients who received 2 or more nusinersen doses and completed the efficacy assessment on day 92. One patient with 3 SMN2 copies, who had a baseline CHOP-INTEND score of 64 points (i.e., maximum score), was excluded from the CHOP-INTEND analysis. The mean change in the CHOP-INTEND score was +11.5 points (P = 0.008 vs. baseline). The CHOP-INTEND score is expected to decrease in SMA Type 1 patients based on a natural history study that showed a decline of 1.27 points per year. Thirteen patients in the nusinersen 12 mg group had 2 SMN2 copies, and 7 achieved a CHOP-INTEND score of greater than 40 points, a score that is rarely achieved in this population. Seven patients died or required permanent ventilatory support, including 2/4 in the nusinersen 6 mg/12 mg group and 5/16 in the nusinersen 12 mg group. The median age of death or permanent ventilation was not reached at the time of the interim analysis. The probability of survival without permanent ventilation was greater in nusinersen-treated patients with 2 SMN2 copies versus historical controls (log-rank test, P = 0.0014) but details of this analysis were unclear. An autopsy was conducted in 3 patients, and more SMN2 transcripts obtained from thoracic spinal cord tissue contained exon 7 (50% to 69%) compared with 15% to 26% in untreated controls. All patients experienced at least 1 adverse event, but most were mild or moderate and consistent with adverse events expected in infants with SMA. No clinically significant changes related to laboratory parameters, neurologic exam, or vital signs occurred. (Finkel, 2017)

Experimental Investigational, Unproven Uses
There is insufficient evidence to support safety and efficacy of nusinersen in SMA Type 0, 2, 3, or 4.

An open-label, single-dose study evaluated nusinersen 1 mg, 3 mg, 6 mg, or 9 mg in children (N = 28) with SMA Type 2 (54%) or Type 3 (46%). The mean age at baseline was 6.1 years (range, 2-14). This study did not evaluate the labeled nusinersen dose (i.e., 12 mg). The study was designed to evaluate nusinersen safety and pharmacokinetics, and some preliminary efficacy outcomes were reported. Efficacy appeared dose-related and there were no dose-limiting toxicities. The authors recommended evaluating nusinersen at doses higher than 9 mg in future studies. (Chiriboga, 2015)

Four additional unpublished studies evaluated nusinersen efficacy in infants and children with SMA. (clinicaltrials.gov, 2017; PR Newswire, 2017) Interim efficacy analyses of these studies provide preliminary evidence supporting nusinersen efficacy in children age 2 to 14 years of age with SMA Type 2 or 3 and in infants with homozygous SMN1 deletion or mutation and 2 or 3 SMN2 copies who are not yet exhibiting SMA symptoms. (Bertini, 2016; Darras, 2016) The FDA product label refers to open-label, uncontrolled trials demonstrating benefit in some individuals who had or were likely to develop Type 1, 2, or 3 SMA (symptomatic individuals who were 30 days to 15 years old at the time of their first dose and pre-symptomatic individuals who were 8-42 days at the time of their first dose). (Biogen Inc., 2016) No studies evaluating nusinersen enrolled patients older than 18 years of age.

Coding/Billing Information

Note: 1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Covered when medically necessary:

HCPCS Codes	Description
J3490	Unclassified drugs

References

1. Arnold WD, Kassar D, Kissel JT. Spinal muscular atrophy: diagnosis and management in a new therapeutic era. Muscle Nerve. 2015;51(2):157-167.

2. Bertini E, Hwu W-L, Reyna SP, investigators eaNs. Nusinersen in presymptomatic infants with spinal muscular atrophy (SMA): interim efficacy and safety results from the phase 2 NURTURE study. Paper presented at: 21st Internationl Congress of the World Muscle Society; October 8, 2016; Granada, Spain.

3. Biogen Inc. Spinraza (nusinersen) injection, for intrathecal use [product information]. Cambridge, MA: Biogen Inc.; December 2016.

4. Center for Drug Evaluation and Research (CDER). Nusinersen (Spinraza): medical review(s): application number 209531. Food and Drug Administration website. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/209531Orig1s000MedR.pdf. Published December 1, 2016 (a). Accessed April 24, 2017.

5. Center for Drug Evaluation and Research (CDER). Nusinersen (Spinraza): statistical review(s): application number 209531. Food and Drug Administration website. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/209531Orig1s000StatR.pdf. Published November 30, 2016 (b). Updated January 18, 2017. Accessed January 24, 2017.

6. 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.

7. Clinicaltrials.gov. Search - ISIS 396443. National Institutes of Health website. https://clinicaltrials.gov/ct2/results?term=ISIS+396443&Search=Search. Published 2017. Accessed January 27, 2017.

8. Cuisset JM, Estournet B. Recommendations for the diagnosis and management of typical childhood spinal muscular atrophy. Rev Neurol (Paris). 2012;168(12):902-909.

9. Darras BT. Spinal muscular atrophies. Pediatr Clin North Am. 2015;62(3):743-766.

10. Darras BT, Chiriboga CA, Montes J, et al; CS2 and CS12 Study Investigators. Nusinersen in treatment-naive patietns with later-onset spinal muscular atrophy (SMA): efficacy results from a phase 1b/2a multicentre study (CS2) and its open-label extension (CS12). Paper presented at: 21st Internationl Congress of the World Muscle Society; October 8, 2016; Granada, Spain.

11. 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. 2017;388(10063):3017-3026.

12. Glanzman AM, O'Hagen JM, McDermott MP, et al. Validation of the Expanded Hammersmith Functional Motor Scale in spinal muscular atrophy type II and III. J Child Neurol. 2011;26(12):1499-1507.

13. Kolb SJ, Kissel JT. Spinal muscular atrophy. Neurol Clin. 2015;33(4):831-846.

14. Kuntz N, Farwell W, Zhong ZJ, et al; ENDEAR study group. Nusinersen in treatment of infantile-onset spinal muscular atrophy (SMA): study design and initial interim efficacy and safety findings from the phase 3 ENDEAR study. Paper presented at: 21st Internationl Congress of the World Muscle Society; October 8, 2016; Granada, Spain.

15. Mazzone E, Montes J, Main M, et al. Old measures and new scores in spinal muscular atrophy patients. Muscle Nerve. 2015;52(3):435-437.

16. PR Newswire. Ionis pharmaceutical completes target enrollment for nusinersen phase 3 study, CHERISH, in children with spinal muscular atrophy [press release]. Carlsbad, CA: PR Newswire; January 12, 2016. http://www.prnewswire.com/news-releases/ionis-pharmaceuticals-completes-target-enrollment-for-nusinersen-phase-3-study-cherish-in-children-with-spinal-muscular-atrophy-300202857.html. Accessed January 30, 2017.

17. Rigo F, Chun SJ, Norris DA, et al. Pharmacology of a central nervous system delivered 2'-O-methoxyethyl-modified survival of motor neuron splicing oligonucleotide in mice and nonhuman primates. J Pharmacol Exp Ther. 2014;350(1):46-55.

18. Sarnat HB. Disorders of neuromuscular transmission and of motor neurons. In: Kliegman RM, Stanton BF, St. Geme JW, III, Schor NF, Behrman RE, eds. Nelson Textbook of Pediatrics. 20th ed. Philadelphia, PA: Elsevier; 2016:2991-2999.

19. Tisdale S, Pellizzoni L. Disease mechanisms and therapeutic approaches in spinal muscular atrophy. J Neurosci. 2015;35(23):8691-8700.

The registered marks "Cigna" and the "Tree of Life" logo are owned by Cigna Intellectual Property, Inc., licensed for use by Cigna Corporation and its operating subsidiaries. All products and services are provided by or through such operating subsidiaries and not by Cigna Corporation. Such operating subsidiaries include Connecticut General Life Insurance Company, Cigna Health and Life Insurance Company, Cigna Behavioral Health, Inc., Cigna Health Management, Inc., and HMO or service company subsidiaries of Cigna Health Corporation.