nusinersen (Spinraza™)

Policy # 00550
Original Effective Date: 04/19/2017
Current Effective Date: 05/16/2018

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage
Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider nusinersen (Spinraza™)‡ for the treatment of spinal muscular atrophy (SMA) to be **eligible for coverage.**

Patient Selection Criteria
Coverage eligibility for nusinersen (Spinraza) will be considered when the following criteria are met:

Initial

- Patient has a diagnosis of spinal muscular atrophy established by, or in consultation with a neuromuscular specialist or neurologist and confirmed by either :
    - SMA diagnostic test results confirming 0 copies of *SMN1*; OR
    - Molecular genetic testing of 5q SMA for any of the following:
        - Homozygous gene deletion; or
        - Homozygous conversion mutation; or
        - Compound heterozygote; AND
- Documentation of genetic test confirming 2 or more copies of *SMN2*; AND
  *(Note: This specific patient criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met)*
- Onset of SMA-associated signs and symptoms at or before 20 months of age; AND
  *(Note: This specific patient criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met)*
- The patient is not currently enrolled in a clinical trial for any experimental therapy for SMA; AND
  *(Note: This specific patient criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met)*
- The medication will be administered by or under the direction of a healthcare professional experienced in performing lumbar punctures; AND
- The requested dose is consistent with the Food and Drug Administration (FDA)-approved dosing of 12 milligrams (mg) administered with 4 loading doses; the first 3 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.

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Continuation

- The "initial" criteria are met; AND
- There is documentation of clinically significant improvement in SMA-associated symptoms (for example, progression, stabilization, or decreased decline in motor function) compared to the predicted natural history trajectory of disease; AND
  *(Note: This specific patient criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met)*
- Dosing will be in accordance with FDA-approved labeling: maximum dosing of 12mg every 4 months starting 4 months after the last loading dose.

When Services Are Considered Not Medically Necessary
Based on review of available data, the Company considers the use of nusinersen (Spinraza) when the number of copies of *SMN2* criteria are not met, symptom onset criteria are not met (as noted above), OR the patient is enrolled in a clinical trial to be **not medically necessary.****

Based on review of available data, the Company considers the use of nusinersen (Spinraza) when there is NO 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 to be **not medically necessary.****

When Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of nusinersen (Spinraza) when the patient selection criteria are not met (except those denoted as **not medically necessary****) to be **investigational.***

Based on review of available data, the Company considers the use of nusinersen (Spinraza) for indications that are not FDA approved to be **investigational.***

Background/Overview

Spinraza is a *SMN2*-directed antisense oligonucleotide indicated for the treatment of SMA in pediatric and adult patients. Spinraza is administered intrathecally at 12 mg per administration. Spinraza is initiated with four loading doses. The first three loading doses should be administered at 14 day intervals. The fourth loading dose should be administered 30 days after the 3rd dose; a maintenance dose should be given once every 4 months thereafter.

Spinal Muscular Atrophy
SMA is an inherited disorder (autosomal recessive) that occurs due to homozygous deletions or variants in the *SMN1* gene. As a consequence of absent or low levels of the *SMN1* protein, the motor neurons in the

spinal cord degenerate resulting in atrophy of the voluntary muscles of the limbs and trunk. *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. Spinraza is a synthetic genetic material that is 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*.

Despite being a rare disease, SMA is the most common genetic cause of death in infants. The incidence of spinal muscular atrophy is estimated to be 1 per 6,000 to 10,000 live births and is estimated to impact as many as 10,000 to 25,000 children and adults in the United States. The carrier frequency is 1 in 40 to 1 in 60, equating to approximately 6,000,000 carriers in the United States. SMA is classified into 5 main categories (Types 0-IV) based on the age at onset of symptoms. Generally, early onset of disease directly correlates to severity of symptoms 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 I SMA is the most common form of SMA and is categorized by SMA symptom onset at or before 6 months of age.

- 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: Onset within 6 months after birth and symptoms progress rapidly, with most infants dying before 1 year of age from respiratory failure. About 60% of patients with SMA constitute this phenotype.
- Type II: Onset is within 6 to 18 months with 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: Onset is after 18 months of age. Lifespan is not affected, with wide-ranging reductions 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: Onset usually presents in the third decade of life and is otherwise similar to type III SMA.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

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

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. FDA approval status, nationally accepted standards of

medical practice and accepted standards of medical practice in this community, Blue Cross and Blue Shield Association technology assessment program (TEC) and other non-affiliated technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

Spinraza was studied in a multicenter, randomized, double-blind, sham-procedure controlled study in 121 symptomatic infants (symptom onset before 6 months of age). Patients also had 2 copies of *SMN2*. Patients were randomized to either receive Spinraza or a sham injection. The primary endpoint assessed at the time of the interim analysis was the proportion of responders: patients with an improvement in motor milestones according to section 2 of the Hammersmith Infant Neurologic Exam (HINE). A greater percentage of patients who received Spinraza achieved a motor milestone response versus those that received the sham procedure control (40% vs. 0%, $p<0.0001$).

Currently, the evidence for use of Spinraza in Type II or III SMA consists of 4 single-arm studies and 1 double-blind randomized controlled trial. The single-arm studies included small numbers of patients and used multiple doses of Spinraza, but the results of those trials did not stratify by dose or type of SMA. The randomized, controlled trial evaluated 126 nonambulatory patients with genetic documentation 5q SMA with the onset of signs and symptoms at more than 6 months and between ages 2 and 12 years at screening as well as the presence of the following features at screening: the ability to sit independently, no history of the ability to walk independently, and a Hammersmith Functional Motor Scale—Expanded (HFMSE) score between 10 and 54. Children were excluded if they had a severe contracture, evidence of severe scoliosis on radiography, respiratory insufficiency, or a gastric tube placed to provide adequate nutrition. Participants were randomized 2:1 to receive either Spinraza or a sham injection. The primary end point was change in HFMSE score compared with baseline. HFMSE scores range from 0 to 66, with higher scores indicating better motor function. A higher percentage of children in the nusinersen group (57%) than in the control group (26%; $p<0.001$) had an increase from baseline to month 15 in the HFMSE score of at least 3 points, which was considered meaningful.

There are currently no studies assessing the safety and efficacy of Spinraza in patients with Type 0 or IV SMA. Therefore, the criteria for coverage presented in this medical policy represent coverage for types I, II, and III SMA only. More information is needed to assess the safety and clinical utility of Spinraza in broader patient populations of SMA.

References

1. Spinraza [package insert]. Biogen, Inc. Cambridge, Massachusetts. Updated December 2017.
2. Spinraza [dossier]. Biogen, Inc. Cambridge, Massachusetts. Updated December 2016.
3. Spinraza. Express Scripts Drug Evaluation. Updated January 2017.
4. Blue Cross and Blue Shield Association. Medical Policy Reference Manual, "Nusinersen for Spinal Muscular Atrophy", Policy # 5.01.28. April 2018.
5. 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 USA.* May 25 1999;96(11):6307-6311.
6. 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.

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Policy History

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04/06/2017 Medical Policy Committee review
04/19/2017 Medical Policy Implementation Committee approval. New policy.
05/03/2018 Medical Policy Committee review
05/16/2018 Medical Policy Implementation Committee approval. Updated policy to include patients with later-onset SMA due to results of the CHERISH trial.
Next Scheduled Review Date: 05/2019

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2017 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	No codes
HCPCS	J3490, J3590 Code deleted eff 1/1/18: C9489 Code added eff 1/1/18: J2326
ICD-10 Diagnosis	G12.0-G12.9

*****Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. FDA and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means

of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:

1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.