

[TEMPLATE

Letter of Medical Necessity:

Use of SPINRAZA® (nusinersen) for Spinal Muscular Atrophy
(Appealing a Clinical Criteria-Based Denial)]

Date:

[Name of Medical Director] RE: Patient Name [_____]

[Health Plan] Policy Number [_____]

[Address] Claim Number [_____]

[City, State, Zip] Diagnosis [_____]

ICD-10-CM Code [_____]

[Note: This appeal letter should be written after fully reviewing the health plan's denial letter and medical policy for SPINRAZA.]

Dear [Health Plan]:

I am writing on behalf of [patient name] to request reconsideration of a denial of coverage for SPINRAZA® (nusinersen), a United States Food and Drug Administration (FDA)–approved treatment for spinal muscular atrophy (SMA) in pediatric and adult patients.

As a board certified [field of certification] with [#] years caring for patients with SMA, I have prescribed SPINRAZA for this patient based on my clinical judgment and expertise. However, you have indicated that SPINRAZA is not covered by [patient's health plan] because [reason for denial letter from patient's explanation of benefits]. The approval of coverage is requested because I believe that treatment with SPINRAZA is medically necessary for [patient name].

To illustrate the appropriateness of this treatment, I would like to provide important details relevant to this particular patient, as well as information about SMA and SPINRAZA.

1. Patient-Specific Rationale for Treatment

[Note: Exercise your medical judgment and discretion when providing a diagnosis and characterization of the patient's medical conditions. Provide clinical rationale that is specific to the reason that the request was denied (eg, age at onset of SMA symptoms or current age at treatment initiation, SMA type, SMN2 copy number, ventilation status).]

In brief, based on the clinical data available to date, it is my medical opinion that initiating treatment with SPINRAZA for **[patient name]** is medically appropriate and necessary and that the procedures required for its administration should be a covered and reimbursed service. Below, this letter outlines **[patient name]**'s medical history and prognosis and the rationale for treatment with SPINRAZA.

[The following section is to be completed by the physician based on the patient's medical history and prognosis.]

2. Summary of Patient's Medical History [You may want to include]:

- Patient's diagnosis and current condition
- Relevant medical history
- Previous therapies the patient has undergone for the symptoms associated with his or her condition
- Patient's response to these therapies
- Overview of the patient's current abilities to perform daily activities and level of mobility and independence, if applicable

[Note: Include any information required by the health plan's medical policy that was omitted in the original request/submission.]

3. Patient's Prognosis

[Summary of the patient's likely prognosis without SPINRAZA treatment vs the patient's prognosis with SPINRAZA treatment.]

4. SMA Pathophysiology

SMA is a genetic neuromuscular disease characterized by degeneration of motor neurons in the anterior horn of the spinal cord. SMA is characterized by progressive symmetrical weakness and atrophy of the proximal voluntary muscles of legs, arms, and, eventually, the entire trunk. Some infants and children affected by SMA develop profound deficits in motor function and miss several developmental milestones. SMA is among the leading genetic causes of infant mortality.

SMA is a single disease caused by a single genetic deficit regardless of type, presentation, and age of onset. SMA results from the deletion and/or mutation of the survival motor neuron 1 (*SMN1*) gene. The *SMN* gene is present in two copies on chromosome 5: the *SMN1* gene and the *SMN2* gene. Nearly all patients with SMA have deletions of exon 7 in both copies of the *SMN1* gene, but a small percentage possess 1 mutated copy of the *SMN1* gene. Unlike the *SMN1* gene, mutations in the second *SMN* gene, the *SMN2* gene, do not determine the development of SMA. Although there is at least 1 copy of the *SMN2* gene present in patients with SMA, copy numbers vary within the population. The number of *SMN2* gene copies has been shown to correlate with disease types and the severity of SMA (eg, patients with SMA Type 2 or 3 are likely to have 2 to 4 copies of the *SMN2* gene, while patients with SMA Type 1 have 1 to 3 copies); however, it is not an absolute predictor of the type of SMA. Not all of the *SMN2* gene copies in an individual may be equivalent regarding the amount of functional protein they produce; therefore, in many cases the number of *SMN2* gene copies is not a predictor of clinical severity of SMA.

5. About SPINRAZA

SPINRAZA is a treatment approved by the FDA indicated for SMA in pediatric and adult patients. SPINRAZA has been studied across multiple clinical trials in patients with varying types of SMA, including presymptomatic and symptomatic infantile-onset and later-onset SMA. The patients in these studies had or were likely to develop SMA Type 1, 2, or 3. The overall findings of the controlled trial support the effectiveness of SPINRAZA across the range of patients with SMA and appear to support the early initiation of treatment with SPINRAZA. These findings are supported by open-label, uncontrolled clinical trials in infantile-onset SMA.

6. Dosing Schedule

SPINRAZA is administered by, or under the direction of, healthcare professionals experienced in performing lumbar punctures. Treatment begins with 4 loading doses; the first 3 loading doses should be administered at 14-day intervals, and the fourth loading dose should be administered 30 days after the third dose. A maintenance dose is administered once every 4 months thereafter.

Conduct the following laboratory tests at baseline and prior to each dose of SPINRAZA and as clinically needed:

- Platelet count
- Prothrombin time, activated partial thromboplastin time
- Quantitative spot urine protein testing

7. Administration of SPINRAZA

In clinical trials, SPINRAZA has been administered in a hospital outpatient setting by, or under the direction of, a healthcare professional with experience in the lumbar puncture procedure. Administration of SPINRAZA may require additional medical procedures, including sedation/anesthesia and/or imaging (eg, ultrasound) to aid in the lumbar puncture.

[Insert more detail lower in the letter when discussing individual patient

needs as appropriate; fill in relevant services with rationale about why the services are clinically appropriate for each patient.]

8. SPINRAZA Clinical Trial Program

SPINRAZA has been evaluated in clinical trials involving a range of patients, from presymptomatic infants to patients 16 years of age at time of treatment initiation.

Controlled Phase 3 Studies

The efficacy of SPINRAZA was demonstrated in two phase 3, randomized, double-blind, sham procedure–controlled clinical trials (ENDEAR and CHERISH) in 247 patients with symptomatic infantile-onset (most likely Type 1) or later-onset (Type 2 and Type 3) SMA.

ENDEAR

The ENDEAR study was conducted over 13 months in 121 patients with symptomatic infantile-onset SMA (symptom onset before 6 months of age). Patients were aged ≤ 7 months at the time of first dose and were deemed most likely to develop SMA Type 1. Patients were randomized 2:1 to receive either SPINRAZA or a sham injection. Primary endpoints of the trial included time to death or permanent ventilation and the proportion of patients meeting the criteria for motor milestone responder using the Hammersmith Infant Neurological Examination (HINE) Section 2.

CHERISH

The CHERISH study was conducted over 15 months in 126 patients aged 2 years to 12 years with symptomatic later-onset SMA (symptom onset after 6 months of age). Patients were randomized 2:1 to receive either SPINRAZA or a sham injection. The primary endpoint of the trial was the least-squares mean change from baseline in the total Hammersmith Functional Motor Scale—Expanded (HFMSE) score at 15 months.

Supportive Open-Label Studies

In addition to ENDEAR and CHERISH, the efficacy of SPINRAZA was also evaluated in open-label clinical trials conducted in patients with presymptomatic and symptomatic infantile SMA, as well as later-onset SMA. The patients in these studies had or were likely to develop SMA Type 1, 2, or 3.

9. Summary of Clinical Trials for SPINRAZA

Information about the following clinical trials for SPINRAZA is available at clinicaltrials.gov.

Study	Phase	Description	Status	Published?
ENDEAR (NCT02193074)	3	Randomized, sham-controlled trial in infants with SMA	Completed	Yes
CHERISH (NCT02292537)	3	Randomized, sham-controlled trial in children with SMA	Completed	Yes
Supporting Open-Label Studies				
SHINE (NCT02594124)	3	Open-label extension for participants in the ENDEAR, CHERISH, and EMBRACE studies	Active, not recruiting	No
EMBRACE (NCT02462759)	2	Open-label, multidose trial in infants and children who did not qualify for ENDEAR or CHERISH	Completed	No
NURTURE (NCT02386553)	2	Open-label study in genetically diagnosed presymptomatic infants with SMA	Active, not recruiting	No
CS3A (NCT01839656)	2	Open-label, multidose trial in infants with SMA to assess tolerability and pharmacokinetics	Completed	Yes
CS12 (NCT02052791)	1	Open-label safety and tolerability study in patients with SMA who previously participated in the CS2 or CS10 studies	Completed	Yes
CS10 (NCT01780246)	1	Open-label safety and tolerability study in patients with SMA who previously participated in the CS1 study	Completed	Yes
CS2 (NCT01703988)	1	Open-label safety, tolerability, and dose-range finding study of multiple doses in patients with SMA	Completed	Yes

CS1 (NCT01494701)	1	Open-label safety, tolerability, and dose-range finding study in patients with SMA	Completed	Yes
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10. Top-Level Summary of Efficacy Data From Phase 3 and Supportive Open-Label Studies

ENDEAR

In the final analysis of the controlled, phase 3 ENDEAR study in infantile-onset SMA, there was a statistically significant reduction in the risk of death or permanent ventilation in SPINRAZA-treated patients compared with untreated patients (HR=0.53; $P=0.005$). Additionally, a higher proportion of SPINRAZA-treated patients achieved a HINE Section 2 motor milestone response compared with untreated patients; this difference was statistically significant ($P<0.0001$). HINE Section 2 (primary endpoint) evaluates 7 different areas of motor milestone development, with a maximum score between 2 and 4 points for each depending on the milestone, and a total maximum score of 26. A treatment responder was defined as any patient with at least a 2-point increase (or maximal score of 4) in the ability to kick (consistent with improvement by at least 2 milestones) or at least a 1-point increase in the motor milestones of head control, rolling, sitting, crawling, standing, or walking (consistent with improvement by at least 1 milestone). To be classified as a responder, patients needed to exhibit improvement in more categories of motor milestones than worsening.

At the final analysis, the study also assessed treatment effects on the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND), which is an evaluation of motor skills in patients with infantile-onset SMA. The results indicated that a higher proportion of SPINRAZA-treated patients had a ≥ 4 -point improvement from baseline in CHOP INTEND scores compared with untreated patients; this difference was statistically significant ($P<0.0001$).

CHERISH

In the final analysis of the controlled, phase 3 CHERISH study in later-onset SMA, a statistically significant improvement in HFMSE scores from baseline to month

15 was observed in SPINRAZA-treated patients compared with untreated patients ($P=0.0000001$). The greatest improvements in the HFMSE score over the 15-month period were observed in younger children and in those who received treatment soon after symptom onset.

Patients receiving SPINRAZA also demonstrated a clinically meaningful change in upper limb function (Revised Upper Limb Module, or RULM, total score) from baseline compared with untreated patients. The RULM evaluates 19 activities reflective of reachable space and activities of daily living.

Supportive Open-Label Studies

The results of the controlled trials in infantile-onset (ENDEAR) and later-onset (CHERISH) patients with SMA were supported by open-label, uncontrolled trials conducted in symptomatic patients with SMA (infantile onset and later onset). Some patients achieved milestones such as ability to sit unassisted, stand, or walk when they would otherwise be unexpected to do so, maintained milestones at ages when they would be expected to be lost, and survived to ages unexpected, considering the number of *SMN2* gene copies of patients enrolled in the studies.

11. Important Safety Information

Coagulation abnormalities and thrombocytopenia, including acute severe thrombocytopenia, have been observed after administration of some antisense oligonucleotides. Patients may be at increased risk of bleeding complications.

In the sham-controlled studies for patients with infantile-onset and later-onset SMA, 24 of 146 SPINRAZA-treated patients (16%) with high, normal, or unknown platelet count at baseline developed a platelet level below the lower limit of normal, compared to 10 of 72 sham-controlled patients (14%). Two SPINRAZA-treated patients developed platelet counts <50,000 cells per microliter, with the lowest level of 10,000 cells per microliter recorded on study day 28.

Renal toxicity, including potentially fatal glomerulonephritis, has been observed after administration of some antisense oligonucleotides. SPINRAZA is present in and

excreted by the kidney. In the sham-controlled studies for patients with infantile-onset and later-onset SMA, 71 of 123 SPINRAZA-treated patients (58%) had elevated urine protein, compared to 22 of 65 sham-controlled patients (34%).

Laboratory testing and monitoring to assess safety should be conducted. Perform a platelet count, coagulation laboratory testing, and quantitative spot urine protein testing at baseline and prior to each dose of SPINRAZA and as clinically needed.

Severe hyponatremia was reported in an infant treated with SPINRAZA requiring salt supplementation for 14 months.

Cases of rash were reported in patients treated with SPINRAZA.

SPINRAZA may cause a reduction in growth as measured by height when administered to infants, as suggested by observations from the controlled study. It is unknown whether any effect of SPINRAZA on growth would be reversible with cessation of treatment.

The most common adverse reactions ($\geq 20\%$ of SPINRAZA-treated patients and $\geq 5\%$ more frequently than in control patients) that occurred in the infantile-onset controlled study were lower respiratory infection and constipation. Serious adverse reactions of atelectasis were more frequent in SPINRAZA-treated patients (18%) than in control patients (10%). Because patients in this controlled study were infants, adverse reactions that are verbally reported could not be assessed. The most common adverse reactions that occurred in the later-onset controlled study were pyrexia, headache, vomiting, and back pain. Post-lumbar puncture syndrome has also been observed after the administration of SPINRAZA.

12. Concluding Remarks

[HCP to insert information relevant to particular case (eg, Given the patient's history, his/her current condition, lack of treatment options for SMA, and the emerging data of the effects of SPINRAZA in patients with SMA, I believe treatment of [patient name] with this product is warranted, appropriate, and

medically necessary. The totality of the data available to date support the potential benefit of treatment with SPINRAZA.)]

Please call my office at [telephone number] if I can provide you with any additional information. I look forward to receiving your approval of this claim.

Sincerely,

[Doctor name and participating provider number]

[Attach supporting documentation such as chart notes, etc]

13. References

1. SPINRAZA [Prescribing Information]. Cambridge, MA: Biogen.
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13. Darras BT, Chiriboga CA, Iannaccone ST, et al; ISIS-396443-CS2/ISIS-396443-CS12 Study Groups. Nusinersen in later-onset spinal muscular atrophy: long-term results from the phase 1/2 studies [published online ahead of print April 24, 2019]. *Neurology*. doi:10.1212/WNL.0000000000007527.