SPINRAZA® (nusinersen) injection 12 mg/5 mL

GUIDE TO DEVELOPING LETTERS OF MEDICAL NECESSITY AND LETTERS OF APPEAL FOR SPINRAZA

INDICATION

SPINRAZA® (nusinersen) is indicated for the treatment of spinal muscular atrophy (SMA) in pediatric and adult patients.

SELECTED 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.

Please see additional Important Safety Information on page 16 and accompanying full Prescribing Information.

INTRODUCTION

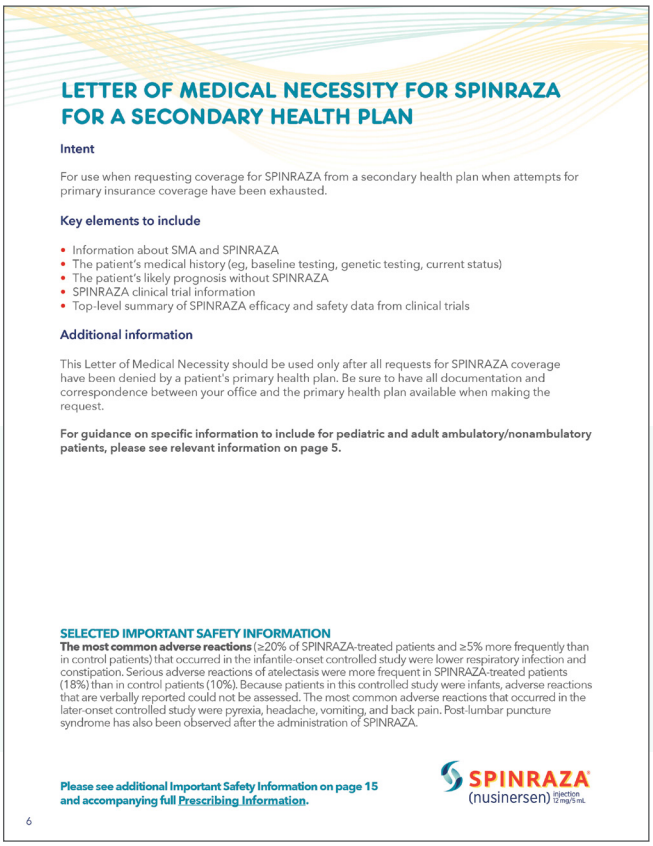
This guide was created as a comprehensive resource of key considerations to use when developing Letters of Medical Necessity and Letters of Appeal for patients who are being prescribed SPINRAZA for SMA.

The sections throughout provide guidance as to exactly who may need these letters written for them and under what circumstances.

How to navigate this guide

Each section of this guide describes a specific Letter of Medical Necessity or Letter of Appeal, further broken down into subsections.

- Intent (the rationale behind writing the letter)
- Key elements to include (information to consider when structuring the letter)
- Additional information (helpful guidance to review before finalizing the letter)



LETTER OF MEDICAL NECESSITY FOR SPINRAZA FOR A SECONDARY HEALTH PLAN

Intent

For use when requesting coverage for SPINRAZA from a secondary health plan when attempts for primary insurance coverage have been exhausted.

Key elements to include

- Information about SMA and SPINRAZA
- The patient's medical history (eg, baseline testing, genetic testing, current status)
- The patient's likely prognosis without SPINRAZA
- SPINRAZA clinical trial information
- Top-level summary of SPINRAZA efficacy and safety data from clinical trials

Additional information

This Letter of Medical Necessity should be used only after all requests for SPINRAZA coverage have been denied by a patient's primary health plan. Be sure to have all documentation and correspondence between your office and the primary health plan available when making the request.

For guidance on specific information to include for pediatric and adult ambulatory/nonambulatory patients, please see relevant information on page 5.

SELECTED IMPORTANT SAFETY INFORMATION

The most common adverse reactions (≥20% of SPINRAZA-treated patients and ≥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.

Please see additional Important Safety Information on page 15 and accompanying full Prescribing Information.

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Using this guide, along with the Letter of Medical Necessity/Appeal Template available at SPINRAZA-hcp.com, can help you craft a concise letter to your patient's health plan.

SMA=spinal muscular atrophy.

SELECTED IMPORTANT SAFETY INFORMATION

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%)

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TABLE OF CONTENTS

These sections are meant to be used as needed when relevant to your situation. Each section in this reference guide is intended to stand alone; therefore, some content may be repeated.

SELECTED IMPORTANT SAFETY INFORMATION

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.

Please see additional Important Safety Information on page 16 and accompanying full Prescribing Information.

SPINRAZA® (nusinersen) injection 12 mg/5 mL

GENERAL GUIDANCE FOR WRITING LETTERS OF MEDICAL NECESSITY AND LETTERS OF APPEAL

An effective letter is tailored to your patient's needs

Be clear about your patient's individual circumstances. The following are key considerations when writing a Letter of Medical Necessity or a Letter of Appeal:

Background on your patient's condition

- Summarize his or her clinical status by citing diagnostic evidence of SMA, including baseline functional exam results and genetic testing results
- If appropriate, list current supportive care management and provide clinical evidence of the patient's disease progression despite supportive care

Why SPINRAZA is, in your opinion, the appropriate treatment choice for your patient

- Provide a clinical justification supporting SPINRAZA treatment for your patient and cite any relevant literature
- State any patient-specific reasons for the treatment choice, such as expected effect of treatment
- Review the health plan's medical policy criteria and point out the specific criteria that your patient meets. Explain why your patient should be excluded from any criteria that he or she does not meet

Providing additional documentation that supports your decision may strengthen your request

Be sure to review the medical policy's requirements to ensure that the requested information is incorporated. Additional documentation may include:

- General medical history listing comorbidities and any medication history, if appropriate
- Letters from other HCPs (such as physical therapists or nurses) who support your treatment choice
- Clinical information regarding your treatment choice, such as the Prescribing Information for SPINRAZA
- Other relevant patient information, as appropriate

See page 14 for information about motor milestone assessments for patients with SMA, and refer to the Clinical Overview guide for data from controlled and uncontrolled open-label trials of SPINRAZA.

HCP=healthcare professional.

SELECTED IMPORTANT SAFETY INFORMATION

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

Please see additional Important Safety Information on page 16 and accompanying full Prescribing Information.

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LETTER OF MEDICAL NECESSITY FOR SPINRAZA TREATMENT-NAIVE PATIENTS

Intent

For use when requesting coverage for patients who have not been previously treated with SPINRAZA.

Key elements to include

- Information about SMA and SPINRAZA
- The patient's medical history (eg, baseline testing, genetic testing, current status)
- The patient's likely prognosis without SPINRAZA
- SPINRAZA clinical trial information
- Top-level summary of SPINRAZA efficacy and safety data from clinical trials

Additional information

The information that you include in your letter may vary depending on your patients' ages and individual situations. The following are considerations for different patient situations that you may encounter, which may be included in a Letter of Medical Necessity for each respective patient type.

Pediatric Ambulatory/Nonambulatory Patient With SMA

Various tests can be used to support an SMA diagnosis, including forms of early genetic testing such as prenatal testing or NBS.

- Test scores establishing baseline measurements (eg, HINE-2, CHOP INTEND, WHO)
- HCP observations
- The HCP's opinion of the anticipated course of SMA for the patient with and without treatment
- Clinical trial information demonstrating SPINRAZA efficacy in pediatric patients (eg, ENDEAR)
- State prioritization of NBS measures

Adult Ambulatory/Nonambulatory Patient With SMA

- Test scores establishing baseline measurements (eg, RULM, HFMSE, 6MWT)
- The HCP's opinion of the anticipated course of SMA for the patient with and without treatment
- Clinical trial information demonstrating SPINRAZA efficacy in later-onset SMA
- Additional real-world observational information about SPINRAZA use in adult patients

6MWT=6-Minute Walk Test; CHOP INTEND=Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; ENDEAR=A Phase 3 study to assess the efficacy and safety of nusinersen in infants with spinal muscular atrophy; HFMSE=Hammersmith Functional Motor Scale–Expanded; HINE-2=Hammersmith Infant Neurological Examination Section 2; NBS=newborn screening; RULM=Revised Upper Limb Module; WHO=World Health Organization.

SELECTED IMPORTANT SAFETY INFORMATION

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.

Please see additional Important Safety Information on page 16 and accompanying full Prescribing Information.

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LETTER OF MEDICAL NECESSITY FOR SPINRAZA FOR A SECONDARY HEALTH PLAN

Intent

For use when requesting coverage for SPINRAZA from a secondary health plan when attempts for primary insurance coverage have been exhausted.

Key elements to include

Information about SMA and SPINRAZA
- The patient's medical history (eg, baseline testing, genetic testing, current status)
- The patient's likely prognosis without SPINRAZA
- SPINRAZA clinical trial information
- Top-level summary of SPINRAZA efficacy and safety data from clinical trials

Additional information

This Letter of Medical Necessity should be used only after all requests for SPINRAZA coverage have been denied by a patient's primary health plan. Be sure to have all documentation and correspondence between your office and the primary health plan available when making the request.

For guidance on specific information to include for pediatric and adult ambulatory/nonambulatory patients, please see relevant information on page 5.

SELECTED IMPORTANT SAFETY INFORMATION

The most common adverse reactions (≥20% of SPINRAZA-treated patients and ≥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.

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LETTER OF APPEAL WHEN SPINRAZA AUTHORIZATION HAS BEEN DENIED

Intent

For use when appealing a denial of initial coverage or reauthorization for SPINRAZA. In preparation for writing this letter, it is important to double-check the policy requirements and the rationale for the denial.

Key elements to include

Patient information, such as name, policy number, and case or claim number
- Reason for the denial as listed in the denial letter
- The patient's medical history and current condition
- The reason you disagree with the denial
- Explanation of the medical necessity for SPINRAZA
- Patient-specific reasons for choosing SPINRAZA, such as expected effect of treatment
- Indication for SPINRAZA
- Additional information to support your treatment decision

Additional information

Providing additional documentation may help justify the use of SPINRAZA

Additional information to help strengthen your patient's appeal may include:
- The patient's medical records
- Appropriate laboratory test results, including genetic testing results
- Pertinent or relevant office notes
- Letters from other HCPs and members of the care team, including but not limited to physical therapists, occupational therapists, respiratory therapists, and dietitians who support your treatment choice
- Published clinical studies documenting the effectiveness of SPINRAZA
- Additional real-world observational information about SPINRAZA use in adult patients
- Examples of other health plan policies in which the patient would be approved for SPINRAZA

When submitting an appeal, timing is critical. Refer to the denial letter to find out the timelines for submitting an appeal.

SELECTED 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.

Please see additional Important Safety Information on page 16 and accompanying full Prescribing Information.

SPINRAZA® (nusinersen) injection 12 mg/5 mL

LETTER OF MEDICAL NECESSITY FOR SPINRAZA REAUTHORIZATION

Intent

For patients continuing on SPINRAZA, it is necessary to renew the authorization for SPINRAZA after the initial coverage period ends. This period may vary depending on the health plan.

Key elements to include

- Information about SMA and SPINRAZA
- A thorough review of motor milestone assessments in SMA
- The patient's medical history (eg, baseline testing, genetic testing, current status)
- The patient's response to SPINRAZA treatment as evidenced by motor milestone results
- Information contributing to the functional measurements compared with baseline
  - Depending on the patient, treatment response may be indicated by an improvement in physical functioning, maintenance of an existing level of functioning, or a slowing of functional decline
- Rationale for continuing treatment
- The patient's likely prognosis without SPINRAZA

Additional information

- When translating test scores in a Letter of Medical Necessity for SPINRAZA Reauthorization for your patient, highlight any improvements in functional measurements compared with baseline. Any improvement may be significant to the patient and contrary to the natural history of the disease; therefore, it is important to document these changes for the health plan to support the reauthorization of SPINRAZA treatment
- Remember, because the criteria of SMA functional tests vary, you can outline cumulative gain in function that the patient achieved according to earlier tests. For example, document how a pediatric patient has gained the ability to hold up his or her head according to HINE-2 even if the patient has also just recently achieved hand grip according to CHOP INTEND
- In addition, children with advanced SMA may not express improvements from baseline based on the traditional scales, but rather may show
  - Subtle improvements due to preservation of residual distal muscles
  - Subtle changes that may be relevant to the patient or caregiver
- Additionally, consider the time it will take for reauthorization of SPINRAZA when planning maintenance dosing. It is good practice to keep in mind the dosing schedule for SPINRAZA and the patient's start date, as they serve as reminders to prepare the documents necessary for reauthorization

See page 13 for dosing and administration information for SPINRAZA.

SELECTED IMPORTANT SAFETY INFORMATION

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.

Please see additional Important Safety Information on page 16 and accompanying full Prescribing Information.

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LETTER OF MEDICAL NECESSITY FOR TREATMENT-EXPERIENCED SPINRAZA PATIENTS SWITCHING FROM OTHER SMA THERAPIES

Intent

For use when requesting coverage for patients who have been previously treated with SPINRAZA, changed to another SMA therapy, and are switching back to SPINRAZA.

Key elements to include

- Information about SMA and SPINRAZA
- A thorough review of motor milestone assessments in SMA
- The patient's medical history including baseline testing, genetic testing, and current status
- The patient's treatment history, including details of previous SPINRAZA treatment and other SMA treatments, and when the last dose of SPINRAZA was received
- Appropriate laboratory test results
- Information contributing to the functional measurements compared with baseline during initial SPINRAZA treatment and subsequent SMA treatment(s)
  - Depending on the patient, treatment response may be indicated by a change in physical functioning, maintenance of an existing level of functioning, or a change in functional decline
- Rationale for previous treatment change from SPINRAZA to other SMA therapy
- Rationale for switch back to SPINRAZA
- The patient's presumed prognosis without SPINRAZA
- Additional information to support your treatment decision

Additional information

Providing additional documentation may help justify the use of SPINRAZA

Additional information to help strengthen your patient's appeal may include:

- The patient's medical records
- Letters from other HCPs and members of the care team, including but not limited to physical therapists, occupational therapists, respiratory therapists, and dietitians who support your treatment choice
- Published clinical studies documenting the effectiveness of SPINRAZA
- Supporting information regarding treatment plan (eg, loading vs maintenance dosing)
  - The need for loading doses may depend on when the last SPINRAZA dose was received

SELECTED IMPORTANT SAFETY INFORMATION

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%).

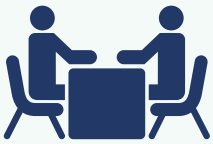
Please see additional Important Safety Information on page 16 and accompanying full Prescribing Information.

Additional information (cont'd)

- Remember, because the criteria of SMA functional tests vary, you can outline cumulative change in function that the patient achieved according to earlier tests both while on SPINRAZA and other SMA treatment(s)
  - Document how an adult patient performed according to the RULM scale or the 6-minute walk test, including any changes in functional abilities
  - Document how a pediatric patient performed according to the HFMSE or CHOP INTEND scale, including any changes in functional abilities

BIOGEN RESOURCES

Biogen offers various resources to help facilitate insurance authorization for SPINRAZA for appropriate patients. These resources include the following:



Rare Disease Reimbursement Managers (RDRMs)
- Assist with navigating the reimbursement process
- Provide guidance on procurement methods
- Educate on claim forms and coding/billing
- Support interactions with health plans on behalf of patients

Rare Disease Account Executives (RDAEs)
- Primary contact for HCPs
- Help answer questions about SPINRAZA
- Share clinical information about SPINRAZA
- Assist in minimizing nonclinical barriers to access

Family Access Managers (FAMs)
- Primary point of contact for patients and caregivers
- Educate about the PA process
- Support in the event of escalations

Lead Case Managers (LCMs)
- Primary call center associate at SMA360°™*
- Assist in understanding the patient's benefits
- Assist in finding an affordable way for patients to start and continue treatment
- Collaborate to obtain PAs
- Provide support for denied claims
- Supply background and resources for referral to third-party charity organizations

PA=Prior Authorization.

*SMA360° services from Biogen are available only to those who have been prescribed SPINRAZA. SMA360° is intended for US residents only.

SELECTED IMPORTANT SAFETY INFORMATION

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.

Please see additional Important Safety Information on page 16 and accompanying full Prescribing Information.

APPENDIX

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

Please see additional Important Safety Information on page 16 and accompanying full Prescribing Information.

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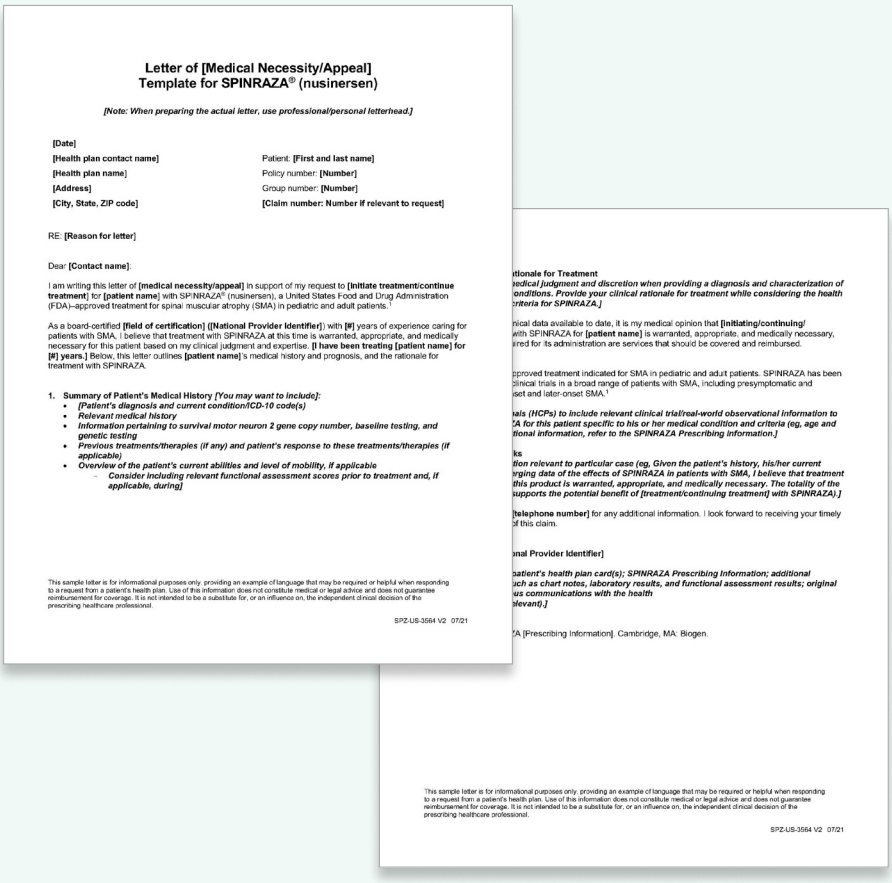
LETTER OF MEDICAL NECESSITY/APPEAL TEMPLATE

This Letter of Medical Necessity/Appeal Template is intended to be used as a guide to help you develop a letter to be submitted to the insurance provider on behalf of your patient. Remember to include the relevant health plan information and patient information (eg, policy number and/or claim number).

Depending on the purpose of your letter and the patient about whom you are writing, you should tailor each section so that it aligns with the Letter of Medical Necessity/Appeal Template as appropriate.



Letter of [Medical Necessity/Appeal]
Template for SPINRAZA® (nusinersen)

[Note: When preparing the actual letter, use professional/personal letterhead.]

[Date]

[Health plan contact name]	Patient: **[First and last name]**
[Health plan name]	Policy number: **[Number]**
[Address]	Group number: **[Number]**
[City, State, ZIP code]	**[Claim number: Number if relevant to request]**

RE: **[Reason for letter]**

Dear **[Contact name]**:

I am writing this letter of **[medical necessity/appeal]** in support of my request to **[initiate treatment/continue treatment]** for **[patient name]** with SPINRAZA® (nusinersen), a United States Food and Drug Administration (FDA)–approved treatment for spinal muscular atrophy (SMA) in pediatric and adult patients.[1]

As a board-certified **[field of certification]** (**[National Provider Identifier]**) with **[#]** years of experience caring for patients with SMA, I believe that treatment with SPINRAZA at this time is warranted, appropriate, and medically necessary for this patient based on my clinical judgment and expertise. **[I have been treating [patient name] for [#] years.]** Below, this letter outlines **[patient name]**'s medical history and prognosis, and the rationale for treatment with SPINRAZA.

1. **Summary of Patient's Medical History** ***[You may want to include]:***
   - ***[Patient's diagnosis and current condition/ICD-10 code(s)***
   - ***Relevant medical history***
   - ***Information pertaining to survival motor neuron 2 gene copy number, baseline testing, and genetic testing***
   - ***Previous treatments/therapies (if any) and patient's response to these treatments/therapies (if applicable)***
   - ***Overview of the patient's current abilities and level of mobility, if applicable***
     - ***Consider including relevant functional assessment scores prior to treatment and, if applicable, during]***

This sample letter is for informational purposes only. providing an example of language that may be required or helpful when responding to a request from a patient's health plan. Use of this information does not constitute medical or legal advice and does not guarantee reimbursement for coverage. It is not intended to be a substitute for, or an influence on, the independent clinical decision of the prescribing healthcare professional.

SPZ-US-3564 V2 07/21

tionale for Treatment
edical judgment and discretion when providing a diagnosis and characterization of onditions. Provide your clinical rationale for treatment while considering the health riteria for SPINRAZA.]

nical data available to date, it is my medical opinion that **[initiating/continuing/** with SPINRAZA for **[patient name]** is warranted, appropriate, and medically necessary, ired for its administration are services that should be covered and reimbursed.

pproved treatment indicated for SMA in pediatric and adult patients. SPINRAZA has been clinical trials in a broad range of patients with SMA, including presymptomatic and set and later-onset SMA.[1]

ials (HCPs) to include relevant clinical trial/real-world observational information to A for this patient specific to his or her medical condition and criteria (eg, age and tional information, refer to the SPINRAZA Prescribing Information.]

ks
tion relevant to particular case (eg, Given the patient's history, his/her current rging data of the effects of SPINRAZA in patients with SMA, I believe that treatment this product is warranted, appropriate, and medically necessary. The totality of the supports the potential benefit of [treatment/continuing treatment] with SPINRAZA).]

[telephone number] for any additional information. I look forward to receiving your timely of this claim.

nal Provider Identifier]

atient's health plan card(s); SPINRAZA Prescribing Information; additional uch as chart notes, laboratory results, and functional assessment results; original us communications with the health levant).]

A [Prescribing Information]. Cambridge, MA: Biogen.

This sample letter is for informational purposes only. providing an example of language that may be required or helpful when responding to a request from a patient's health plan. Use of this information does not constitute medical or legal advice and does not guarantee reimbursement for coverage. It is not intended to be a substitute for, or an influence on, the independent clinical decision of the prescribing healthcare professional.

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The Letter of Medical Necessity/Appeal Template can be found at **SPINRAZA-hcp.com**.

SELECTED IMPORTANT SAFETY INFORMATION

Cases of rash were reported in patients treated with SPINRAZA.

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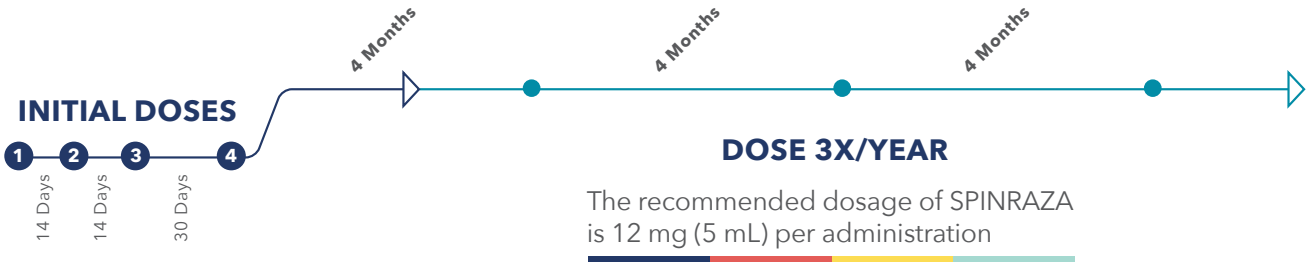
SPINRAZA® (nusinersen) injection 12 mg/5 mL

DOSING INFORMATION FOR SPINRAZA[1]

SPINRAZA is injected into the cerebrospinal fluid and targets central nervous system tissues

- SPINRAZA is administered intrathecally
- Begin treatment with 4 loading doses. The first 3 doses should be administered at 14-day intervals. The fourth dose should be administered 30 days after the third dose. After the starting dose period, a dose should be administered once every 4 months
  - 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



- Sedation should be considered as indicated by the clinical condition of the patient
- Ultrasound or other imaging techniques should be used to guide intrathecal administration
- Maintenance dosing consists of 3 doses per year (after the first year)
- Reauthorization intervals should align with dosing schedule

SELECTED IMPORTANT SAFETY INFORMATION

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.

Please see additional Important Safety Information on page 16 and accompanying full Prescribing Information.

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MOTOR MILESTONE ASSESSMENT TESTS FOR SMA

There are a variety of functional tests that can be used to assess patients with SMA. Because motor milestones in infants and children with SMA vary significantly, there is not one standardized functional assessment used in clinical practice.[2,3]

These tests evaluate a range of motor functions and are appropriate for different populations with SMA.[3]

Summary of motor function tests for SMA

The Hammersmith Infant Neurological Examination Section 2 (HINE-2) **Age 2 months to 24 months**		Measures neuromuscular development in infants, including voluntary grasp, sitting, ability to kick, crawling, head control, standing, rolling, and walking.[4] A 1-point increase in HINE score represents increased level of ability.[5]
The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND) **Infants and children**		The first SMA-specific test to assess patients with limited motor function; can measure response to gains and losses in motor function over time.[3] Includes 16 items that may be graded from 0 to 4, contributing to a total score of 64 points.[3]
World Health Organization (WHO) Motor Milestones **Age 4 months to 24 months**		Compares the actual windows of childhood development with those used in assessments of motor skills.[6] The 6 WHO motor milestones are measured and compared across similar populations in different countries.[6]
The Revised Upper Limb Module (RULM) **Age >36 months**		Assesses upper limb function in ambulatory and nonambulatory patients with SMA.[7] Nineteen items are graded on a 3-point scale, with a score of 0 (unable), 1 (able with modification), or 2 (able, no difficulty). The maximum total score is 37, which includes a can/cannot score of 1 or 0 for the first item in the assessment.[7]
The Hammersmith Functional Motor Scale–Expanded (HFMSE) **Ambulatory patients with SMA Type 2 or Type 3**		Assesses gross motor function of ambulatory patients.[2] A 2-point change is clinically relevant (eg, a child who was previously not able to crawl has improved crawling ability).[8]
6-Minute Walk Test (6MWT) **Ambulatory patients**		Measures the distance in meters that a patient can walk unassisted.[9] Participants walk unaided for 25 meters; distance walked over 6 minutes, distance covered each minute (patients can rest without sitting), and time to complete the 25-meter course are recorded. Falls are also recorded.[9]

SELECTED IMPORTANT SAFETY INFORMATION

The most common adverse reactions (≥20% of SPINRAZA-treated patients and ≥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%).

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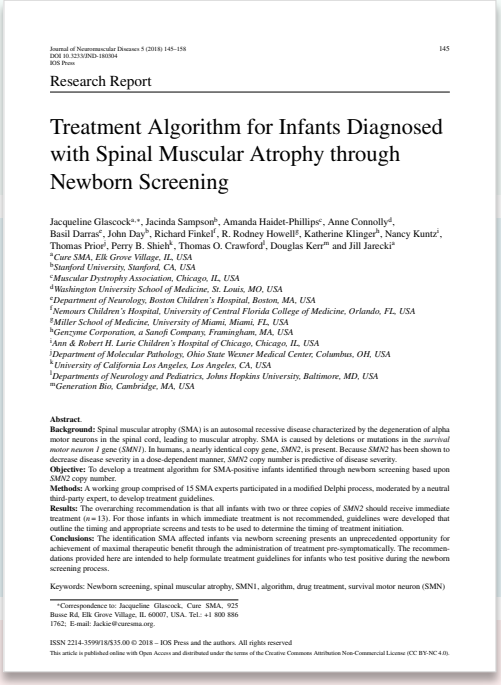
A CONSENSUS REPORT RECOMMENDS TREATMENT FOR PRESYMPTOMATIC INFANTS WITH SMA[10,11]

The SMA NBS Multidisciplinary Working Group (15 members) formulated treatment guidelines for individuals who have a positive SMA NBS test result.

The Biogen trials with infants with SMA (ENDEAR and NURTURE) provided evidence of the importance of NBS and early treatment.

"The NURTURE study results are a strong indicator of the importance of NBS in achieving maximal efficacy with *SMN* enhancers in treating SMA."

"The working group unanimously recommends immediate treatment for these individuals to achieve a maximal response to treatment, as supported by the strong positive results arising from pre-symptomatic infants in the NURTURE trial for individuals predicted to manifest SMA by qualifying genotype who have either two and three copies of *SMN2*."



Journal of Neuromuscular Diseases 5 (2018) 145–158 145
DOI 10.3233/JND-180304
IOS Press

Research Report

Treatment Algorithm for Infants Diagnosed with Spinal Muscular Atrophy through Newborn Screening

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Abstract.
Background: Spinal muscular atrophy (SMA) is an autosomal recessive disease characterized by the degeneration of alpha motor neurons in the spinal cord, leading to muscular atrophy. SMA is caused by deletions or mutations in the *survival motor neuron 1* gene (*SMN1*). In humans, a nearly identical copy gene, *SMN2*, is present. Because *SMN2* has been shown to decrease disease severity in a dose-dependent manner, *SMN2* copy number is predictive of disease severity.
Objective: To develop a treatment algorithm for SMA-positive infants identified through newborn screening based upon *SMN2* copy number.
Methods: A working group comprised of 15 SMA experts participated in a modified Delphi process, moderated by a neutral third-party expert, to develop treatment guidelines.
Results: The overarching recommendation is that all infants with two or three copies of *SMN2* should receive immediate treatment ($n = 13$). For those infants in which immediate treatment is not recommended, guidelines were developed that outline the timing and appropriate screens and tests to be used to determine the timing of treatment initiation.
Conclusions: The identification SMA affected infants via newborn screening presents an unprecedented opportunity for achievement of maximal therapeutic benefit through the administration of treatment pre-symptomatically. The recommendations provided here are intended to help formulate treatment guidelines for infants who test positive during the newborn screening process.

Keywords: Newborn screening, spinal muscular atrophy, SMN1, algorithm, drug treatment, survival motor neuron (SMN)

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In 2019, the working group updated their recommendation: "The working group has updated our position to a recommendation for immediate treatment for infants diagnosed with SMA via NBS with four copies of *SMN2* (n = 12)."

NURTURE=A Phase 2 study of multiple doses of nusinersen delivered to infants with genetically diagnosed and presymptomatic spinal muscular atrophy; SMN=survival motor neuron; SMN2=survival motor neuron 2 gene.

SELECTED IMPORTANT SAFETY INFORMATION

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.

Please see additional Important Safety Information on page 16 and accompanying full Prescribing Information.

INDICATION

SPINRAZA® (nusinersen) is indicated for the treatment of spinal muscular atrophy (SMA) in pediatric and adult patients.

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 (≥20% of SPINRAZA-treated patients and ≥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.

Please see accompanying full Prescribing Information.

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SPINRAZA® (nusinersen) injection 12 mg/5 mL

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