A GUIDE TO SPINRAZA REIMBURSEMENT

IMPORTANT INFORMATION TO HELP NAVIGATE THE ACCESS AND REIMBURSEMENT PROCESS

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.

Please see additional Important Safety Information on page 75 and accompanying full Prescribing Information.
INTRODUCTION

WELCOME

SPINRAZA is a US Food and Drug Administration (FDA)-approved treatment indicated for spinal muscular atrophy (SMA) in pediatric and adult patients. Biogen is committed to providing detailed information to assist in obtaining reimbursement for SPINRAZA, drug administration, and related ancillary services.

We have developed this guide in conjunction with our support service, SMA360°, to provide you with the information you need to help with the reimbursement process for SPINRAZA. SMA360° offers individualized support to help your patients and their families throughout the treatment process.

The information in this guide is intended for informational purposes only and does not represent legal or billing advice. For specific guidance in this area, consult your own legal/billing advisor and billing/coding specialist because it remains your responsibility to ensure the accuracy of the claims your office submits. The content herein is based on information current as of April 2019, and may have changed.

Any product, ancillary supplies, or services received free of charge cannot be billed to third-party payers because doing so could be a violation of federal and/or state laws and/or third-party-payer requirements.

SPINRAZA SUPPORT AND RESOURCES

SMA360° is here for your patients

Biogen’s SMA360° program offers comprehensive and individualized support to help patients with SMA and their families navigate nonmedical barriers to access. Services include logistical assistance, product education, insurance benefits investigation, and financial assistance. A complete list of the SMA360° offerings can be found at SPINRAZA-hcp.com/support.

SMA is a highly variable disease and each patient will have his or her own unique set of needs. Your patients or their caregivers may feel like they could use a helping hand. Biogen has a team that will be there for them throughout the SPINRAZA journey.

Please remember that you should be the primary resource for any questions related to SMA and SPINRAZA. Additional information about the services provided by SMA360° are included in this guide.

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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.

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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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SMA360° IS AVAILABLE TO ASSIST YOU

SMA360° team members, such as Rare Disease Reimbursement Managers (RDRMs), are available to assist your practice or site of care (SOC) by providing nonclinical education and support to help overcome access challenges.

RARE DISEASE REIMBURSEMENT MANAGER

The RDRM is responsible for helping you and your staff navigate the reimbursement and administrative processes for SPINRAZA.

The RDRM can help

• Educate you and your staff on SPINRAZA procurement methods
• Provide enhanced education on claims forms and coding/billing
• Support your team’s interactions with health plans
TABLE OF CONTENTS

Overview of the Reimbursement Process for SPINRAZA ............................................................... 6

Site-of-Care Considerations ....................................................................................................... 12

Investigating Benefits and Obtaining Authorization .............................................................. 18

Navigating Financial Assistance Options ............................................................................... 35

Ordering SPINRAZA .................................................................................................................. 40

Submitting Claims for SPINRAZA and Related Services ...................................................... 42

Medicare and SMA ..................................................................................................................... 61

Appendix ..................................................................................................................................... 72

- Sample SPINRAZA Start Form
- Sample SPINRAZA Copay Reimbursement Form
- Sample Letters of Medical Necessity
- Indication and Important Safety Information
- References

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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.

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OVERVIEW OF THE REIMBURSEMENT PROCESS FOR SPINRAZÄ® (nusinersen)

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OVERVIEW OF THE REIMBURSEMENT PROCESS FOR SPINRAZA

The following pages highlight key phases of the reimbursement process for SPINRAZA, including steps for starting a patient on therapy, as well as the information needed to submit a claim for reimbursement. Biogen is here to support you in the administration of SPINRAZA and timely submission of claims for adjudication.

This overview also informs various stakeholders involved in the care of patients receiving SPINRAZA. Your Biogen representative is available to assist you with any questions you may have about the process.

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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A Benefits Investigation will help determine payer requirements based on the patient’s specific insurance plan benefits and the individualized care plan

**A.** Conduct a Benefits Investigation to help identify the following for SPINRAZA administration and related services:

- **Coverage requirements**, including precertification and/or medical documentation; referral restrictions; and observation stay rules
- **Patient out-of-pocket (OOP)** costs such as annual deductible vs amount met to date, coinsurance and/or copay, and annual OOP maximum vs amount met to date
- **State and/or network considerations**
  - Participation status of the institution/practices and participating providers
  - Coverage restrictions and related exceptions process
  - OOP costs and related exceptions process
  - Secondary coverage coordination of benefits and reimbursement/payment methodology from payers
- **Billing guidelines**
  - All documentation required to be submitted with the claim
  - National Drug Code (NDC) number reporting requirements

Approval of appropriate authorization(s) will provide payer coverage documentation before treatment initiation

**B.** Contact the patient’s payer(s) directly to submit necessary documentation in order to obtain authorization for SPINRAZA administration and related services, such as

- PA/precertification form(s) and/or Letter of Medical Necessity
- Out-of-state and/or out-of-network exception request and related documentation

**C.** If your authorization or exception request has been denied, locate the appeal process and timeline in the denial letter. Contact the payer for instructions if they are not documented for you.

Your RDRM and Family Access Manager (FAM) are available to assist you with any questions you may have about this process.

*For additional details, please refer to pages 18-33 of this guide.*

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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.

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The SMA360°* team will help connect the enrolled patient with appropriate financial assistance programs and provide insurance counseling, if needed

A. The SMA360° team identifies appropriate financial assistance options for eligible patients and assists with program enrollment and any related additional documentation‡:
   • $0 Drug Copay Program
   • $0 Procedure Copay Program
   • Third-Party Funding Assistance

B. The SMA360° team offers insurance counseling to the patient’s family (if applicable), including
   • Summary of current insurance status
   • Review of potential alternative or supplemental sources of insurance coverage (eg, Medicaid)

The SMA360° team can coordinate SPINRAZA administration logistics

C. The SMA360° team coordinates logistics with the patient’s family and the SOC in preparation for the SPINRAZA administration visit

For additional details, please refer to pages 35-38 of this guide.

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‡Other programs may also be available for your patients.

COMPREHENSIVE SUPPORT FOR YOUR PATIENT IS AVAILABLE
The SMA360° team will contact the enrolled patient’s family to help set expectations.
We understand that for a caregiver or an individual living with SMA, life can be challenging. SMA360° is a support service from Biogen created to help families navigate the following areas of the treatment process with SPINRAZA:
   • Treatment logistics
   • Insurance and financial assistance

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Administer SPINRAZA according to the Prescribing Information and individualized care plan

- SPINRAZA is administered intrathecally by, or under the direction of, healthcare professionals (HCPs) with experience performing lumbar punctures.

Following payer billing guidelines can facilitate claim processing and prompt payment

A. Submit claim(s) to the patient’s payer(s) for SPINRAZA and related services according to the billing guidelines identified through the Benefits Investigation

For additional details, please refer to pages 42-57 of this guide.

B. Schedule the next patient visit for SPINRAZA administration

Payer remittance monitoring will be critical for ensuring appropriate payment

C. Monitor payer remittance for the submitted claim(s)

D. Submit appeal with required documentation within filing timelines if the claim is denied

E. Submit eligible OOP expenses to copay assistance or charitable funding programs, if applicable

For additional details, please refer to pages 58-59 of this guide.

If you have any questions throughout this process, call SMA360® at 1-844-4SPINRAZA (1-844-477-4672), Monday through Friday, from 8:30 AM to 8:00 PM ET, or contact your Biogen representative.

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SITE-OF-CARE CONSIDERATIONS

Please see additional Important Safety Information on page 75 and accompanying full Prescribing Information.
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ADDITIONAL CONSIDERATIONS FOR PAYER REIMBURSEMENT

- The facility services may be subject to some form of global payment rule or prospectively set reimbursement rates (e.g., global surgery payment, diagnosis-related group [DRG]-based payment, Enhanced Ambulatory Patient Groups [EAPG] payment)

- The payment for SPINRAZA may be separate or may be bundled within a prospectively set rate (e.g., DRG-based rate, EAPG rate per diem rate)

OUTPATIENT OBSERVATION STAY INSIGHTS

An observation stay is a hospital outpatient service that can be ordered by physicians to allow for medical evaluation and/or testing in order to determine whether a patient may require an inpatient stay. For example, if a patient experiences a complication after an outpatient surgery, his or her physician may order outpatient observation services to allow for additional monitoring after the postoperative recovery period.

The following are some features of an observation stay that could affect billing:

- A patient may occupy any bed in the hospital, but with outpatient status
- Outpatient status has important implications for hospital reimbursement and patient OOP costs
- The stay is typically completed within 24 to 48 hours, after which time the patient can be admitted as an inpatient or discharged
- Payers may cover different lengths of outpatient observation stays
  - Medicaid may allow up to 48 hours; other private payers may cover only 23 hours
- It is important to verify the requirements for an outpatient observation stay with each insurance carrier

SOC IMPLICATIONS FOR RELEVANT FINANCIAL ASSISTANCE PROGRAMS

There are several financial assistance programs available to eligible patients to support the administration of SPINRAZA. It is important to note to families that the SOC does not limit the patient’s eligibility for Biogen financial assistance programs. Biogen has several assistance programs for the SPINRAZA administration procedure and drug. See page 36 for more information. For more information on third-party funding assistance, contact SMA360°* at 1-844-4SPINRAZA (1-844-477-4672), Monday through Friday, from 8:30 AM to 8:00 PM ET.

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PATIENT CARE CHECKLIST

Below is a sample checklist for your consideration.

☑ Determine if any ancillary services may be needed to support SPINRAZA administration via intrathecal injection

☐ Anesthesia
☐ Lumbar puncture
☐ Ultrasound
☐ Fluoroscopy
☐ Other

☑ Evaluate the need for and the feasibility of an outpatient observation stay post injection

☐ Observation stay as a possibility in lieu of inpatient admission

☑ Document the administration plan for the dosing schedule

☐ Dates of loading doses
☐ Dates of maintenance doses (if applicable)

☑ Select the setting and the SOC for SPINRAZA administration

Outpatient Setting
☐ Hospital outpatient off-campus clinic
☐ Hospital outpatient on-campus facility
☐ Hospital-based ASC
☐ Freestanding ASC
☐ Physician office

Inpatient Setting
☐ Inpatient hospital facility

Other Setting
☐ Other facility

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PATIENT CARE CHECKLIST (cont’d)

Below is a sample checklist for your consideration.

- Identify which providers/provider practice groups will offer professional services related to SPINRAZA administration
  - Neurology
  - Radiology
  - Anesthesiology
  - Other

- Coordinate with the patient and his or her caregiver to confirm site selection and logistics and to help set appropriate expectations
  - Treatment process and related timelines
  - Current payer coverage situation and any anticipated changes
  - Potential financial assistance needs
  - SMA360° support services available for patients and their families

- Suggest SMA360°™* support services, which may be available to help the patient’s family understand and navigate the treatment process
  - Provide the patient’s family with the SPINRAZA Start Form, assist in completing the patient portion, and review caregiver consent (see page 72 of the Appendix for a sample Start Form)
    - Your practice or facility should complete the HCP portion of the SPINRAZA Start Form. Be sure to include the provider’s signature in the Prescriber Authorization section. Fax the completed Start Form to 1-888-538-9781 or email it to StartForm@Biogen.com
  - If signed consent is provided, advise the patient’s family that a FAM from Biogen will assist in coordinating the logistics of treatment, such as insurance and financial considerations, if needed

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INVESTIGATING BENEFITS AND OBTAINING AUTHORIZATION

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INVESTIGATING BENEFITS AND OBTAINING AUTHORIZATION

A Benefits Investigation is an important step to complete for patients prescribed SPINRAZA to determine drug and ancillary procedure medical coverage. It will help define payer requirements based on the patient’s specific insurance plan benefits and his or her individual needs.

BEGINNING THE BENEFITS INVESTIGATION

A Benefits Investigation is a process that enables a provider to determine benefit design, coverage requirements, and coding guidance. It is important to note that there are many variables associated with each patient’s benefits, and there may be differences by payer, state, general benefit design, and SOC. For SPINRAZA treatment, there may be patients who travel to an SOC that is out of state and/or out of network for his or her payer. It is important to capture this information upfront during the Benefits Investigation process so that your practice or facility can submit the claim to be reimbursed for acquiring SPINRAZA, as well as for its administration.

The following is basic patient and provider information that your practice or facility will need to gather to initiate the Benefits Investigation process.

BASIC PATIENT INFORMATION

- **Contact information**
  - □ Patient name
  - □ Date of birth
  - □ Phone number
  - □ Address

- **Insurance information**
  - □ Policyholder name
  - □ Policy start and end dates
  - □ Member number
  - □ Group number
  - □ Type(s) of plan(s) (eg, HMO, PPO, POS, EPO, Medicaid)
  - □ Primary, secondary, and tertiary insurance information (eg, commercial, Medicaid)

EPO = exclusive provider organization; HMO = health maintenance organization; POS = point of service; PPO = preferred provider organization.

COMPREHENSIVE SUPPORT IS AVAILABLE THROUGHOUT THE BENEFITS INVESTIGATION

SMA360° is a support service from Biogen created to help navigate the complexities of treatment logistics, insurance, and financial assistance. We understand that your patients’ needs are unique, and the SMA360° team is here to help.

We can answer any questions you may have about obtaining preauthorization or precertification, and advise you on how to best navigate the complexities of Benefits Investigation or any unforeseen bumps in the road to approval.

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**BASIC PROVIDER INFORMATION**

- **Physician prescribing SPINRAZA**
  - Physician name
  - NPI #
  - Tax ID #

- **Physician(s) administering SPINRAZA (if different from the prescriber)**
  - Physician name
  - NPI #
  - Tax ID #

- **Site of care administering SPINRAZA**
  - Practice/facility name
  - NPI #
  - Site of care/place of service

**BASIC COVERAGE INFORMATION**

Contact the payer to gather the following information:

- **Coverage**
  - Covered
  - PA required
  - Quantity

- **Patient cost**
  - Office visit copay or coinsurance
  - Drug cost copay or coinsurance
  - Deductible
  - OOP maximum
  - Pharmacy capitation

**KEEPING ACCURATE RECORDS OF A BENEFITS INVESTIGATION**

It is important to document each communication exchange that your practice or facility has with insurance companies. You may be communicating with them several times during the Benefits Investigation. When you do, be sure to record the following:

- Date of communication
- Time of communication
- Person(s) you spoke with
- Contact information (direct phone line, email)
- Communication preference (fax, email)
- Reference number for the call

NPI=National Provider Identifier.

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KEY CONSIDERATIONS FOR A BENEFITS INVESTIGATION (cont’d)

Coding and claims submission details

Specific coding and billing requirements may vary by payer
- Clarify the requirements for reporting an NDC number in a medical claim
- Check if any specific documentation is required to be submitted with the claim (eg, clinical records, drug invoice)

Patient financial responsibility

Patient OOP costs may vary based on the specific benefit design, SOC, and out-of-state/out-of-network restrictions
- Determine the patient’s annual deductible and how much has been met to date
- Record the coinsurance and/or copay that will apply for SPINRAZA and related services
- Determine the patient’s annual OOP maximum and how much has been met to date

SMA360° PATIENT SUPPORT SERVICES AND BENEFITS INVESTIGATION

SMA360° will also investigate the insurance benefits in order to help the patient and/or his or her family understand their current coverage and OOP costs, educate them about the financial assistance options, and offer counseling regarding the possibility of changing or adding insurance benefits, if needed. These services help supplement the Benefits Investigation conducted by your practice or facility. If you have any questions throughout this process, call SMA360° at 1-844-4SPINRAZA (1-844-477-4672), Monday through Friday, from 8:30 AM to 8:00 PM ET, or contact your Biogen representative.

Remember to reverify your patient’s benefits prior to each dose of SPINRAZA, as the insurance coverage may have changed since the patient’s last procedure. Remind your patients of the importance of immediately informing you and SMA360° of any insurance changes or updates to avoid unanticipated delays in therapy.

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KEY CONSIDERATIONS WHEN MEDICAL NECESSITY IS REQUIRED

The following are situations in which your practice or facility may need to demonstrate medical necessity for SPINRAZA during an appeal. The level of information in the letter will vary based on key areas that the payer requires be addressed to demonstrate medical necessity. Your practice or facility can customize the Letter of Medical Necessity based on the specific needs of the payer and the situation (see page 74 for a sample of a Letter of Medical Necessity).

The payer requires that a preauthorization/PA be obtained before the treatment will be approved

- Based on the payer’s requirements for authorization, demonstrate that the treatment is medically necessary based on the patient’s diagnosis, clinical presentation, baseline motor functional testing, duration of symptoms, and current supportive care management

The payer reviewed your request for a preauthorization/PA and denied it, determining that the treatment was not medically necessary

- Determine if the reason for the denial was clerical, clinical, or benefit-driven
  - If the denial was for clerical reasons, immediately resubmit the request with the proper information
  - If the denial was for clinical reasons, determine what additional information may be required to demonstrate medical necessity
  - If the denial was for benefit reasons, call the payer to determine if an exception to the benefit is allowed and the process for such an exception (e.g., no out-of-network benefits but only experienced provider is out of network)
- Emphasize in your resubmission that your practice or facility believes the treatment to be medically necessary for your patient

SELECTED IMPORTANT SAFETY INFORMATION

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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.

Please see additional Important Safety Information on page 75 and accompanying full Prescribing Information.
The payer has a policy for treatment and administration services for SPINRAZA, but your patient does not meet the requirements. However, the prescribing physician feels that the treatment is medically necessary

- Point out that the patient requires an exception to the plan’s policy and provide the clinical rationale demonstrating that treatment with SPINRAZA is clinically appropriate
- Provide documentation or information to demonstrate medical necessity, such as
  - Diagnostic evidence of SMA, including genetic testing
  - Clinical presentation and duration of symptoms
  - Current supportive care management
  - Expectations of therapy and how efficacy will be measured by the clinician
  - Other relevant aspects of patient history

The payer will not cover the treatment and administration services because it will be administered at an out-of-network or out-of-state facility

- Emphasize your opinion that the facility is the most appropriate center to deliver the highly specialized services that may be provided when administering SPINRAZA
- Point out that the patient’s plan does not, in your opinion, currently have an appropriate specialized center to treat SMA in the network and/or state, and that the patient has no other choice but to go out of his or her current network and/or state
- Point out continuity-of-care concerns of switching the patient to a new provider unfamiliar with the patient’s history
- Provide documentation or information to demonstrate medical necessity, such as
  - Name and specialty area of your practice or facility to demonstrate its level of expertise
  - Distance the patient needs to travel to your practice or facility because there are no other specialized facilities in his or her network and/or state
  - Areas of medical specialization and years of experience treating patients with SMA

When an ME/appeal is denied due to clinical reasons and the submission of an exception to benefit request has been disallowed or denied, the prescribing physician may contact the insurance carrier directly to speak with a clinical representative, who is typically a medical director or someone with a medical background. This is called a peer-to-peer discussion.

- A peer-to-peer discussion can be an effective way to help the health plan understand the patient’s unique medical history, relevant clinical factors, and how those factors support treatment with SPINRAZA
- If the HCP is able to obtain the direct contact information for the clinical representative, consider tracking that information to use for future peer-to-peer discussions

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 75 and accompanying full Prescribing Information.
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.

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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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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. These tests evaluate a range of motor functions and are appropriate for different populations with SMA.8

SUMMARY OF MOTOR FUNCTIONAL TESTS FOR SMA

- The Hammersmith Infant Neurological Examination (HINE Section 2)9
  - Ages 2 months to 24 months
  - Measures neuromuscular development in infants, including voluntary grasp, sitting, ability to kick, crawling, head control, standing, rolling, and walking9
  - A 1-point increase in HINE score represents increased level of ability10

- The Children’s Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND)8
  - 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 time8
  - Includes 16 items that may be graded between 0 and 4, contributing to a total score of 64 points8

- The Hammersmith Functional Motor Scale—Expanded (HFMSE)7
  - Ambulatory SMA Type 2 or Type 3 patients
  - Assesses gross motor function of ambulatory patients7
  - A 2-point change is clinically relevant, eg, a child who was previously not able to crawl has increased crawling ability11

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.

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Cases of rash were reported in patients treated with SPINRAZA.

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CLAIM RECONSIDERATION AND APPEALS CHECKLIST

If a claim has been denied, you can request an appeal. There are several common reasons that claims are denied, such as an incorrect patient identification number or omission of a Letter of Medical Necessity. Another reason that a claim may be denied for SPINRAZA is that the product is not yet being covered under the insurer’s coverage benefit. In each of these cases, it is important to consider an appeal.

The following are some considerations for understanding and filing an appeal.

Some top reasons that claims are denied:
- Incorrect codes
- Missing information
- Incorrect product information
- Lack of a Letter of Medical Necessity

If additional information is requested, submit the necessary documentation immediately.

Consider the following to understand the appeals process of each payer:
- Is there a need for a particular form?
- How should the form be sent to the payer?
- Can the appeal take place over the phone via a physician-to-physician call with the payer?
- Who should receive the appeal (name, title, and contact information)?
- What must accompany the appeal (eg, supporting documentation)?
- How long does the appeals process usually take?
- How will I learn about the appeal decision?

Record the correspondence with the payer at every point of the appeals process.

If your claim is denied a second time, determine if a next-level appeal is allowed and carefully submit it within your payer’s timelines. Request assistance from your Biogen representative if needed.

EOB=explanation of benefits; RA=remittance advice.

SELECTED IMPORTANT SAFETY INFORMATION

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ME/APPEAL CONSIDERATIONS FOR PEDIATRIC PATIENTS WITH SMA

For initial authorization for SPINRAZA
Include the following to help support medical necessity when an initial authorization request has been denied:

- Test scores establishing baseline measurements, eg, HINE Section 2, CHOP INTEND, and WHO
- HCP observations not tested, eg, reduction in respiratory infections or lower ventilator setting
- The HCP’s opinion of the anticipated course of SMA for the patient with and without treatment

For continued approval of maintenance therapy with SPINRAZA
When translating test scores into support for an ME or appeal, highlight all improvements in functional measurements compared with baseline. Because the criteria of the SMA functional tests vary, outline cumulative gain in function that the patient achieved according to earlier tests. For example, if a patient has gained the ability to hold up his/her head according to HINE Section 2, note this even if the patient most recently achieved hand grip according to CHOP INTEND. Other considerations include

- Children with advanced SMA may not express improvements from baseline based on the traditional scales, but rather may show
  - Subtle improvements or preservation of residual distal muscles
  - Subtle changes that may impact activities of daily living that are relevant to the patient
- 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 medical necessity of treatment with SPINRAZA

SELECTED IMPORTANT SAFETY INFORMATION
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NAVIGATING FINANCIAL ASSISTANCE OPTIONS

Please see additional Important Safety Information on page 75 and accompanying full Prescribing Information.
NAVIGATING FINANCIAL ASSISTANCE OPTIONS

The SMA360° team can help your patients’ families navigate the cost of treatment with SPINRAZA. Patients may have a copay or coinsurance for the drug and/or for the administration of SPINRAZA after they meet their annual deductible and until they reach the annual limit for their maximum OOP costs.

Biogen believes that cost should not be a barrier to treatment. SMA360° offers personalized insurance and financial assistance to help your patients’ families understand their insurance benefits for SPINRAZA and to identify the most affordable way to start and stay on treatment as prescribed by their doctor.

PATIENT COST-SHARING STRUCTURE CONSIDERATIONS

During the Benefits Investigation, it is important to determine key elements of the cost-sharing structure under the patient’s insurance benefits, including the following:

- **Copay**: Typically, a flat fee that patients pay each time they receive medical care. The copay may be in addition to other OOP costs, such as deductibles and coinsurance, and it varies by benefit structure.

- **Coinsurance**: A beneficiary cost-sharing amount that begins after the deductible is paid. Coinsurance typically is based on a percentage of the cost of services and varies by payer.

- **Deductible**: A predetermined amount of money that the patient must spend before his or her payer benefits take effect.

- **Maximum OOP cost**: An annual limitation on all cost sharing that patients are responsible for under a health insurance plan. This limit does not apply to premiums, balance-billed charges from out-of-network HCPs, or services that are not covered by the plan.

In addition to the Benefits Investigation conducted by your practice or facility, SMA360° will investigate patient benefits in order to be able to inform the patient’s family about potential cost-sharing responsibility and to discuss potential implications.

*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

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INITIATING THE $0 DRUG COPAY PROGRAM FROM BIOGEN

This program generally is available for patients with nongovernmental insurance benefits who have provided consent to Biogen. It covers the amount of cost sharing for SPINRAZA, but does not cover administration-related costs. After conducting a Benefits Investigation, the SMA360° team will contact eligible patients to introduce the program and to complete enrollment.

What your practice or facility needs to do

1. Confirm patient enrollment
   - Confirm that the patient is enrolled in the $0 Drug Copay Program for SPINRAZA for every treatment dose. At enrollment, the patient and HCP will receive a confirmation letter via fax from Biogen. This information also is available through your Biogen representative.
   - Keep the confirmation of enrollment in the patient’s file. If the patient withdraws, Biogen will send a withdrawal letter. This information also is available by calling 1-844-4SPINRAZA (1-844-477-4672).

2. Obtain EOB/RA
   - Locate the EOB/RA demonstrating the patient’s financial responsibility for SPINRAZA.

3. Fill out the Copay Reimbursement Form
   - Fill out the Copay Reimbursement Form.
   - Fax the EOB/RA and the completed Copay Reimbursement Form to Biogen at 1-888-656-4343.
   - Your practice or facility will receive a reimbursement check for plans that cover SPINRAZA under the medical benefit. For plans that cover SPINRAZA under the pharmacy benefit, Accredo SP manages the adjudication via the Rx BIN, PCN, and Group Number.

BIN=bank identification number; PCN=processor control number.

If you have any questions throughout this process, call SMA360° at 1-844-4SPINRAZA (1-844-477-4672) or contact your Biogen representative.

SMA360° offers insurance counseling services to help patients’ families understand their current insurance benefits for SPINRAZA and to provide assistance with changing or adding supplemental insurance benefits, such as Medicaid.

SELECTED IMPORTANT SAFETY INFORMATION

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Please see additional Important Safety Information on page 75 and accompanying full Prescribing Information.
ORDERING SPINRAZA® (nusinersen)

Please see additional Important Safety Information on page 75 and accompanying full Prescribing Information.
ORDERING SPINRAZA

The SMA360°™ team will contact the enrolled patient’s family to coordinate treatment logistics for each SPINRAZA administration visit. It is important for your office to coordinate with your Biogen representative when ordering SPINRAZA so that the patient’s family can be prepared for the visit.

HOW TO ORDER SPINRAZA

CuraScript SD and Accredo SP are the exclusive authorized providers of SPINRAZA. Ordering SPINRAZA is done in the same way as any other product that is administered at your SOC, whether it is an outpatient hospital-based facility, physician office, freestanding ASC, or inpatient hospital facility. SPINRAZA can be ordered directly through CuraScript SD or from Accredo SP. Once the order for SPINRAZA has been submitted to your pharmacy or procurement department, the order for SPINRAZA will be placed.

SPINRAZA ORDERING CHECKLIST

☑ Confirm that your practice or facility is ready to order SPINRAZA
  □ Benefits Investigation has been conducted
  □ Payer approval of appropriate authorizations has been obtained
  □ (Optional) Patient has been enrolled in available financial assistance program(s)

☑ Order SPINRAZA from CuraScript SD or Accredo SP
  □ Follow the standard process for placing a prescription drug order in your practice or facility
    • The SPINRAZA Start Form includes a prescription for SPINRAZA. However, some states may require a separate prescription to be sent to Accredo SP
  □ Your pharmacy or procurement department will need to submit the order form to CuraScript SD
    • 1-855-778-1510 (phone)
    • 1-866-579-4655 (fax)

☑ Coordinate SPINRAZA shipment delivery with the scheduled patient treatment visit
  □ CuraScript SD or Accredo SP will ship SPINRAZA in a temperature-controlled container directly to your practice or facility
  □ Make sure there is a staff member available to accept delivery of SPINRAZA and to transfer the product to a refrigerated space in the pharmacy immediately upon receipt of the drug
  □ Coordinate the treatment procedure for SPINRAZA with your site’s care team, including the pharmacy

For assistance with any step in this process, contact your Biogen representative.

*SMa360° services from Biogen are available only to those who have been prescribed SPINRAZA. SMA360° is intended for US residents only.
†Including off-campus clinic, on-campus facility, hospital-based ASC, and other outpatient outlets operated by a hospital.

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SUBMITTING CLAIMS FOR SPINRAZA® (nusinersen) AND RELATED SERVICES

Please see additional Important Safety Information on page 75 and accompanying full Prescribing Information.
FOLLOWING PAYER BILLING GUIDELINES CAN FACILITATE CLAIM PROCESSING AND PROMPT PAYMENT

When a patient has been administered the SPINRAZA injection and/or a related service, your practice or facility may submit a claim to the patient’s insurance plan. Items included on your claim may depend on the SOC and the billing entity.

- Hospital facilities and hospital-based ASCs may submit a CMS-1450/UB-04 claim form

- Physician office practices may submit a CMS-1500 claim form either for professional services related to drug administration or for the drug and the services related to drug administration

- Freestanding ASCs may submit a CMS-1500 claim form for the medication and the services related to drug administration

The information within this section reviews some of the billing codes relevant for SPINRAZA and the related administration services, as well as key billing considerations across SOCs. However, coding and billing recommendations may vary by payer. Your practice or facility should check directly with the patient’s payer(s) to verify specific coding and billing requirements. Biogen field representatives are available to answer questions and further support the reimbursement process.

SELECTED IMPORTANT SAFETY INFORMATION

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SUMMARY OF RELEVANT CODES FOR SPINRAZA

ICD-10-CM CODE EXAMPLES

<table>
<thead>
<tr>
<th>ICD-10-CM Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>G12.0</td>
<td>Infantile spinal muscular atrophy, type I [Werdnig-Hoffmann]</td>
</tr>
</tbody>
</table>
| G12.1         | Other inherited spinal muscular atrophy  
Adult form spinal muscular atrophy  
Childhood form, type II spinal muscular atrophy  
Juvenile form, type III spinal muscular atrophy [Kugelberg-Welander] |

HCPCS CODE

<table>
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<tr>
<th>HCPCS Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>J2326</td>
<td>Injection, nusinersen, 0.1 mg</td>
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</tbody>
</table>

• Since SPINRAZA has been assigned a permanent J-code, effective January 1, 2018, C9489 should no longer be used.


NDC NUMBER

<table>
<thead>
<tr>
<th>NDC Number</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>64406-058-01</td>
<td>12 mg/5 mL single-dose vial (contains 12 mg of nusinersen solution for intrathecal injection)</td>
</tr>
</tbody>
</table>

Although the FDA uses a 10-digit format when registering NDC numbers, payers often require an 11-digit NDC format on claim forms for billing purposes. It is important to confirm with your payer which NDC format is required. In addition, Medicaid requires that all claims for provider-administered drugs include NDC numbers. This reporting requirement might also be implemented by some commercial payers.23 Guidelines for reporting the NDC number in the appropriate format, quantity, and unit of measure vary by state and by payer and should be reviewed prior to submitting a claim.
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CODING GUIDE FOR MODERATE SEDATION OF LESS THAN 52 MINUTES\textsuperscript{17}

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<thead>
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<th>Total intra-service time for MS*</th>
<th>Patient age</th>
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<th>Code(s)</th>
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<td>Less than 10 minutes</td>
<td>Any age</td>
<td>Not reported separately</td>
<td>Not reported separately</td>
</tr>
<tr>
<td>10-22 minutes</td>
<td>&lt;5 years</td>
<td>99151</td>
<td>99155</td>
</tr>
<tr>
<td>10-22 minutes</td>
<td>5 years or older</td>
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<td>99156</td>
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<tr>
<td>23-37 minutes</td>
<td>&lt;5 years</td>
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<td>99155 + 99157 x 1</td>
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<tr>
<td>23-37 minutes</td>
<td>5 years or older</td>
<td>99152 + 99153 x 1</td>
<td>99156 + 99157 x 1</td>
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<td>38-52 minutes</td>
<td>&lt;5 years</td>
<td>99151 + 99153 x 2</td>
<td>99155 + 99157 x 2</td>
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<tr>
<td>38-52 minutes</td>
<td>5 years or older</td>
<td>99152 + 99153 x 2</td>
<td>99156 + 99157 x 2</td>
</tr>
</tbody>
</table>

*For MS coding of 53 minutes or longer, or for descriptions of individual codes, please refer to page 737 of the CPT coding book CPT\textsuperscript{®} 2019 Professional.

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Please see additional Important Safety Information on page 75 and accompanying full Prescribing Information.
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 75 and accompanying full Prescribing Information.
CODING SUMMARY FOR ELECTRONIC CLAIM SUBMISSION BY OUTPATIENT HOSPITAL-BASED FACILITIES*

The table below provides examples of relevant codes, along with corresponding locations, for paper and electronic claims submitted by outpatient hospital-based facilities for SPINRAZA and related administration services.

Requirements and location of information will vary by payer.

### Examples of Relevant Codes for SPINRAZA and Electronic Billing Locations for Outpatient Hospital-Based Facilities

<table>
<thead>
<tr>
<th>Information</th>
<th>Sample Code(s) or Information</th>
<th>CMS-1450/UB-04 Locator*</th>
<th>Electronic Loop*</th>
<th>Equivalent Segment*</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCPCS Level II Code</td>
<td>J2326</td>
<td>Field 44</td>
<td>2400</td>
<td>SV202-2</td>
</tr>
<tr>
<td>HCPCS Level II Code Units</td>
<td>120</td>
<td>Field 46</td>
<td>2400</td>
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<tr>
<td>Additional Product Information</td>
<td>SPINRAZA 64406-0058-01 12 mg/5 mL, 5 mL intrathecal inj</td>
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<td>2300</td>
<td>NTE</td>
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<tr>
<td>CPT® Code(s)</td>
<td>96450 Other CPT® codes may apply, as appropriate</td>
<td>Field 44</td>
<td>2400</td>
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</tr>
<tr>
<td>ICD-10-CM Code (primary)</td>
<td>G12.0</td>
<td>Field 67</td>
<td>2300</td>
<td>HI01-2</td>
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<td>Bill Type Code</td>
<td>Provider specific†</td>
<td>Field 4</td>
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<tr>
<td>Revenue Code(s)</td>
<td>0361 0636 Other revenue codes may apply, as appropriate</td>
<td>Field 42</td>
<td>2400</td>
<td>SV201</td>
</tr>
</tbody>
</table>

*Including off-campus clinic, on-campus facility, hospital-based ASC, and other outpatient outlets operated by a hospital.

†A 4-digit bill type code documents facility type (second digit after the leading zero), care type (third digit), and the bill sequence for the given episode of care (fourth digit). Relevant examples for outpatient facilities include 013X (hospital outpatient), 074X (clinic outpatient physical therapy [OPT]), and 083X (hospital outpatient ASC), where X represents the sequence of the billing in this particular episode of care (eg, “1” for admit through discharge claim).18

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 75 and accompanying full Prescribing Information.
SAMPLE CMS-1450/UB-04 CLAIM FORM
FOR OUTPATIENT HOSPITAL-BASED FACILITIES*

Field 46: Enter the appropriate number of units of service.

Fields 42 and 43: Enter appropriate revenue codes and corresponding description of service; for example:
- 0636, Pharmacy (ie, drugs requiring detailed coding)
- 0361, Operating room services (ie, minor surgery)

NOTE: Other revenue codes may apply; for example:
- 0331, Radiology/therapeutic (ie, chemotherapy injected)
- 0370, Anesthesia (ie, general classification)
- 0402, Other imaging services (ie, ultrasound)
- 0710, Recovery room

For Field 43, NDC reporting requirements may vary by payer.

Field 67: Enter the appropriate primary ICD-10-CM diagnosis code; for example:
- G12.0, Infantile spinal muscular atrophy, type I (Werdnig-Hoffmann)

Field 4: Enter the appropriate type of bill code; for example:
- 013X, Hospital outpatient
- 074X, Clinic OPT
- 083X, Hospital outpatient (ASC)
"X represents a placeholder for the fourth digit, which indicates the sequence of this bill in this particular episode of care (eg, "1" for admit through discharge claim).

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.

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.

Please see additional important Safety Information on page 75 and accompanying full Prescribing Information.
UNIQUE BILLING CONSIDERATIONS FOR PROFESSIONAL SERVICES

CPT® CODE MODIFIER FOR THE PROFESSIONAL COMPONENT

<table>
<thead>
<tr>
<th>Modifier</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>26</td>
<td>Professional component</td>
</tr>
</tbody>
</table>

For procedure codes with professional and technical components, physician office practices may use the 26 modifier to bill for the professional services component of the procedure performed in the hospital inpatient or outpatient setting.17

CODING SUMMARY FOR ELECTRONIC CLAIM SUBMISSION FOR PROFESSIONAL SERVICES

The table below provides examples of relevant codes, along with corresponding locations, for paper and electronic claims submitted by physician office practices for professional services associated with SPINRAZA administration.

Requirements and location of information will vary by payer.

<table>
<thead>
<tr>
<th>Information</th>
<th>Sample Code(s) or Information</th>
<th>CMS-1500 Location27</th>
<th>Electronic Loop27</th>
<th>Equivalent Segment27</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CPT® Code(s)</strong></td>
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<td>Field 24D</td>
<td>2400</td>
<td>SV101</td>
</tr>
<tr>
<td></td>
<td>76942</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>00635</td>
<td>Other CPT® codes may apply, as appropriate</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ICD-10-CM Code (primary)</strong></td>
<td>G12.0</td>
<td>Field 21A</td>
<td>2300</td>
<td>HI01-2</td>
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<tr>
<td><strong>Place of Service Code</strong></td>
<td>Provider-specific*</td>
<td>Field 24B</td>
<td>2300</td>
<td>CLM05-1</td>
</tr>
</tbody>
</table>

* A 2-digit place of service code documents site of care. Relevant examples for professional services include 19 (off-campus outpatient hospital), 22 (on-campus outpatient hospital), and 21 (inpatient hospital).28

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 75 and accompanying full Prescribing 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 75 and accompanying full Prescribing Information.
UNIQUE BILLING CONSIDERATIONS FOR PHYSICIAN OFFICES AND FREESTANDING ASCs

CODING SUMMARY FOR ELECTRONIC CLAIM SUBMISSION BY PHYSICIAN OFFICES AND FREESTANDING ASCs

The table below provides examples of relevant codes, along with corresponding locations, for paper and electronic claims submitted by physician office practices or freestanding ASCs for SPINRAZA and related administration services.

Requirements and location of information will vary by payer.

<table>
<thead>
<tr>
<th>Information</th>
<th>Sample Code(s) or Information</th>
<th>CMS-1500 Location</th>
<th>Electronic Loop</th>
<th>Equivalent Segment</th>
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</thead>
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<tr>
<td>HCPCS Level II Code</td>
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<td>Field 24D</td>
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<td>SV101</td>
</tr>
<tr>
<td>HCPCS Level II Code Units</td>
<td>120</td>
<td>Field 24G</td>
<td>2400</td>
<td>SV101</td>
</tr>
<tr>
<td>Additional Product Information</td>
<td>SPINRAZA 64406-0058-01 12 mg/5 mL, 5 mL intrathecal inj</td>
<td>Field 19</td>
<td>2300</td>
<td>NTE</td>
</tr>
<tr>
<td>CPT® Code(s)</td>
<td>96450 Other CPT® codes may apply, as appropriate</td>
<td>Field 24D</td>
<td>2400</td>
<td>SV101</td>
</tr>
<tr>
<td>ICD-10-CM Code (primary)</td>
<td>G12.0</td>
<td>Field 21A</td>
<td>2300</td>
<td>HI01-2</td>
</tr>
<tr>
<td>Place of Service Code</td>
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<td>Field 24B</td>
<td>2300</td>
<td>CLM05-1</td>
</tr>
</tbody>
</table>

*A 2-digit place of service code documents site of care. Relevant examples for professional services include 11 (office) and 24 (ASC).28

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 75 and accompanying full Prescribing Information.
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.

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.

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Please see additional Important Safety Information on page 75 and accompanying full Prescribing Information.
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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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Please see additional Important Safety Information on page 75 and accompanying full Prescribing Information.
SAMPLE CMS-1450/UB-04 CLAIM FORM
FOR INPATIENT HOSPITAL FACILITIES

**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 75 and accompanying full Prescribing Information.
CLAIM SUBMISSION AND TRACKING CHECKLISTS

Completing timely and accurate claims can help facilitate prompt payment. In order to help proactively prevent denials and underpayment, it is important to review claims before submitting them to a payer.

CLAIM SUBMISSION CONSIDERATIONS CHECKLIST

Confirm payer requirements

- During the Benefits Investigation process, confirm that you have identified the following:
  - Coverage and any PA restrictions
  - Coding and billing guidelines
  - Required medical documentation

Check claim for accuracy and completeness

- When filling out the claim form, please double-check the following:
  - Patient information (eg, patient name, insurer, subscriber name, date of birth, member ID)
  - Provider information (eg, NPI number, name, address, place of service)
  - Coding (eg, ICD-10, CPT®, revenue, and/or HCPCS codes along with appropriate modifiers)
  - Billing units (consistent with the descriptors for the reported CPT® and/or HCPCS codes)
  - Additional information required by the payer (eg, PA, Tax ID and/or drug NDC number)

Confirm compliance with claim submission rules

- When submitting the claim, be mindful of the following:
  - Required standards for electronic claims
  - Punctuation and character limit requirements
  - Time frame for submitting claims

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.

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Please see additional Important Safety Information on page 75 and accompanying full Prescribing Information.
MEDICARE AND SMA

Please see additional Important Safety Information on page 75 and accompanying full Prescribing Information.
MEDICARE ELIGIBILITY FOR PATIENTS WITH SMA*†

WHO IS ELIGIBLE?

- People younger than 65 years who have received Social Security Disability Insurance (SSDI) benefits for at least 2 years (24 months)\(^3\)0
  - For these patients, enrollment in Medicare is automatic\(^3\)1
- People aged 65 years or older\(^3\)0

- Children with SMA who are younger than 18 years can qualify for Supplemental Security Income (SSI) if they meet SSDI requirements and their income and resources fall within the eligibility limits\(^3\)0
- Children who were receiving benefits as a minor child on a parent’s Social Security record (via SSI) may be eligible to continue receiving benefits on that parent’s record upon reaching age 18 if they are disabled\(^3\)0
  - Marriage of the disabled “adult child” may affect eligibility for this benefit
- Medicare covers about 1 in 4 adults with SMA (aged 18 years and older)

A PERSON CAN QUALIFY FOR SSDI BENEFITS IF

- He or she has a past work history\(^3\)2
- He or she can no longer work due to his or her disability\(^3\)2

- SMA Types 0 and 1 qualify as compassionate allowance for social security disability (1 of more than 200 conditions); it is automatic in many states\(^3\)3
- State-based qualification parameters also apply
- To learn about disability benefits through Social Security, contact 1-800-772-1213 or https://www.ssa.gov/benefits/disability/

HOW PATIENTS APPLY FOR MEDICARE

- Most people with SMA who are receiving SSDI benefits are automatically enrolled in Original Medicare (Parts A and B)\(^3\)1
  - Patients who receive SSDI get Part A at no cost but have to pay a premium for Parts B and D. If patients don’t want the Part B premium automatically deducted from their SSDI, they can call Medicare to opt out of Part B
- Patients will be enrolled by the 25th month of receiving SSDI. They will get their Medicare card in the mail\(^3\)1
- Patients also get a notice in the mail about their Part D drug plan. It will tell them how to review or change it

If patients are not disabled, they will need to enroll in Medicare. They can sign up in 2 ways\(^3\)1:

- Call the Social Security office at 1-800-772-1213
- Sign up online at https://www.ssa.gov/planners/retire/justmedicare.html

*Please note that Maryland follows the terms of the Maryland All-Payer Model and some of the following information may not apply.
†Medicare providers and suppliers are not permitted to bill people enrolled in the Qualified Medicare Beneficiary program for items such as Medicare copays, deductibles, or coinsurance.

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 75 and accompanying full Prescribing Information.
MEDICARE BASICS

HOW DOES MEDICARE WORK?

Medicare has 4 parts to help cover services:

A. **Part A** is hospital insurance. It covers inpatient care in a hospital, nursing home care, hospice care, and home healthcare. **Part A covers SPINRAZA** when patients receive it as an inpatient during a hospital stay.

B. **Part B** is medical insurance. **Part B covers SPINRAZA** when patients receive it as an outpatient, for instance, at an SMA treatment center.

Parts A and B are known as “Original Medicare.” Patients will have Original Medicare unless they choose a Medicare Advantage Plan or other type of Medicare health plan.

C. **Part C** is also called Medicare Advantage. Part C plans are sold by private insurance companies approved by Medicare. These plans include all services covered under Part A and Part B. Part C may offer additional benefits, as well. Patients usually get prescription drug coverage (Part D) through a Medicare Advantage plan. See the following page for more detailed information about Medicare Advantage plans.

D. **Part D** is prescription drug coverage. Part D covers drug costs (pills, self-administered injections, and inhaled treatments). Part D plans are sold by private insurance companies approved by Medicare. **These plans do not cover SPINRAZA**, but they cover other drugs patients may need.

SMA360° can help patients navigate Medicare options. Patients can call 1-844-4SPINRAZA (1-844-477-4672), Monday through Friday, from 8:30 am to 8:00 pm ET.

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 75 and accompanying full Prescribing Information.
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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.

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Please see additional Important Safety Information on page 75 and accompanying full Prescribing Information.
A MEDIGAP POLICY MAY HELP PATIENTS PAY FOR TREATMENT COSTS NOT COVERED BY ORIGINAL MEDICARE

Medicare Supplement Insurance policies, also known as Medigap policies, can help pay some of the costs Original Medicare does not. This includes copayments, coinsurance, and deductibles. Medigap policies are sold by private insurance companies. They must follow federal and state laws.31

Facts about Medigap policies

| Medigap policies are not available to people covered by a Medicare Advantage Plan (Part C)31 | Patients must have Medicare Part A and Part B to have a Medigap Policy31 | Patients cannot purchase a Medigap policy along with a Medicare MSA40 |

CONTINUING SPINRAZA TREATMENT WHEN INSURANCE CHANGES

It is important to track and understand changes in health insurance for your patients with SMA, including primary and secondary insurance plans

- For example, patients with SMA may transition to Medicare from Medicaid; Medicare becomes the primary insurer and Medicaid is the secondary insurer
- Patients with SMA may require authorization for treatment due to the change in health insurance
- Insurance claims submitted to the wrong primary insurer will likely be rejected and will need to be resubmitted to the correct insurer, causing a significant delay in reimbursement

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 75 and accompanying full Prescribing Information.
THE EXTENT OF WHAT MEDICARE COVERS DEPENDS ON WHETHER IT IS PAYING AS A PRIMARY OR SECONDARY PAYER

- Medicare as the primary payer pays up to the limits of its coverage\textsuperscript{31}
  - Hospital coverage (Part A)
  - Physician visits, outpatient services, and physician-administered drugs like SPINRAZA (Part B)
  - Self-administered prescription drugs, which do not include SPINRAZA (Part C)

- Coverage gaps still exist with Medicare as primary payer\textsuperscript{31,41}
  - Patients can cover gaps with secondary payer/supplemental insurance (eg, employer-sponsored health plan, Medigap policy)

- Medicare as the secondary payer
  - Main role is to close the gap in OOP expenses\textsuperscript{31}
  - Pays only if there are costs not covered by the primary insurer\textsuperscript{31}
  - Medicare coinsurance will still apply\textsuperscript{31}
  - Covers claims when primary payment is delayed or in dispute\textsuperscript{42}

SELECTED IMPORTANT SAFETY INFORMATION

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

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Please see additional Important Safety Information on page 75 and accompanying full Prescribing Information.

HOSPITAL REIMBURSEMENT FOR SPINRAZA

SPINRAZA HAS PASS-THROUGH STATUS FOR 340B THROUGH 2020

As of January 1, 2018, Medicare pays an adjusted amount of the average sales price (ASP) minus 22.5% for certain separately payable drugs or biologics acquired through the 340B program and furnished to a Medicare beneficiary by a hospital paid under the Outpatient Prospective Payment System (OPPS) that is not exempt from the payment adjustment policy.25

• However, SPINRAZA has pass-through status through June 30, 2020, and is not subject to this adjusted amount43

• When administered in the outpatient setting, Medicare reimbursement for SPINRAZA is set at ASP+6%25

• The Centers for Medicare & Medicaid Services (CMS) has established the HCPCS informational modifier “TB” for pass-through drugs (assigned status indicator “G”) acquired with a 340B discount at most hospitals25

• On July 1, 2020, if the rule to the 340B program is not revised, SPINRAZA will be reimbursed at ASP minus 22.5% (instead of ASP+6%) for 340B-purchased drugs only for Medicare patients treated at affected sites of care25,43


UNDERSTANDING APCs VS DRGs (BUNDLED PAYMENTS)

• Ambulatory Payment Classifications (APCs) are the government’s way to pay facilities for outpatient services under the Medicare program44

• Hospital-only, OPPS
  – SPINRAZA is allowed separate payment in the hospital outpatient department setting

• No impact on physician payments under the Medicare Physician Fee Schedule

• APC payments are made to the hospital when a Medicare outpatient is discharged or is transferred to another hospital or facility not affiliated with the initial hospital where the patient received outpatient services

• Inpatient stays are paid under DRG methodology rather than APC.44 DRG payments do not allow separate payment for drugs administered during an inpatient stay45

• Medicare inpatient stays are subject to the 3-day rule. All outpatient services during the 3 days prior to an inpatient stay need to be incorporated into the inpatient DRG stay45
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.

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

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Please see additional Important Safety Information on page 75 and accompanying full Prescribing Information.
NATIONAL AND LOCAL COVERAGE DETERMINATIONS

NATIONAL COVERAGE DETERMINATIONS

- CMS contracts with private companies known as MACs to process and pay claims.
- CMS issues National Coverage Determinations (NCDs).
- An NCD describes the circumstances under which a particular item or service (e.g., a drug) is covered nationally under Medicare.
- NCDs apply to all MACs nationwide.
- CMS has not issued an NCD for SPINRAZA.

HOW PART A AND PART B BENEFITS ARE ADMINISTERED UNDER ORIGINAL MEDICARE

MACs process Medicare Part A and Part B (A/B) claims for a defined geographic area or “jurisdiction.”

There are 2 types of MACs:

- A/B MACs process Part A and Part B claims for a defined geographic area servicing institutional providers, physicians, practitioners, and suppliers.
- Durable Medical Equipment (DME) MACs process Medicare Durable Medical Equipment, Orthotics, and Prosthetics (DMEPOS) claims for a defined geographic area servicing suppliers of DMEPOS.

There are 7 A/B MACs covering a total of 12 jurisdictions.

- Claims for SPINRAZA are processed by A/B MACs. Each MAC may have its own rules for coverage, billing/coding, etc.
- Healthcare insurers can be awarded more than 1 jurisdiction to process claim.

MACs AND MEDICAL POLICY

- CMS-issued NCDs apply to all MACs nationwide.
- If an NCD does not exist or needs to be defined further, MACs can issue a Local Coverage Determination (LCD).
- An LCD is a coverage policy representing the MAC’s decision to cover or exclude a particular item or service and is applicable only within its jurisdiction.
- Regional MACs may review SPINRAZA claims on a case-by-case basis until they issue an LCD or CMS issues an NCD with conditions for coverage.

MACs can impact medical policy.

- Establish LCDs
- Handle first-stage appeals process
- Review medical records for selected claims

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 75 and accompanying full Prescribing Information.
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 75 and accompanying full Prescribing Information.
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 75 and accompanying full Prescribing Information.
Please see additional Important Safety Information on page 75 and accompanying full Prescribing Information.
The SPINRAZA Start Form must always be accompanied by the consent information. Please contact your Biogen representative for a copy of this document or download from SPINRAZA-hcp.com.

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.

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.

Please see additional Important Safety Information on page 75 and accompanying full Prescribing Information.
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 75 and accompanying full Prescribing Information.
SAMPLE LETTERS OF MEDICAL NECESSITY

Sample Treatment-Naive Letter

For use when requesting an exception to the plan’s published criteria for SPINRAZA, which may be necessary for certain patients to receive SPINRAZA.

Sample Secondary Payer Authorization Request Letter

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

Sample Reauthorization Letter

For use to help achieve reauthorization for patients who have previously received SPINRAZA.

Please contact your Biogen representative for copies of these documents.

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 75 and accompanying full Prescribing Information.

SPINRAZA® (nusinersen) injection 12 mg/5 mL
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 enclosed full Prescribing Information.
REFERENCES


Please see additional Important Safety Information on page 75 and accompanying full Prescribing Information.
REFERENCES (cont’d)


REFERENCES (cont’d)


43. Hospital Outpatient Prospective Payment and Ambulatory Surgical Center Payment Systems and quality reporting programs, 81 Federal Register 79562 (2016).


HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use SPINRAZA® safely and effectively. See full prescribing information for SPINRAZA.

SPINRAZA (nusinersen) injection, for intrathecal use
Initial U.S. Approval: 2016

INDICATIONS AND USAGE
SPINRAZA is a survival motor neuron-2 (SMN2)-directed antisense oligonucleotide indicated for the treatment of spinal muscular atrophy (SMA) in pediatric and adult patients (1)

DOSAGE AND ADMINISTRATION
SPINRAZA is administered intrathecally (2.1)

Dosing Information (2.1)
- 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.

Important Preparation and Administration Instructions (2.2)
- Allow to warm to room temperature prior to administration
- Administer within 4 hours of removal from vial
- Prior to administration, remove 5 mL of cerebrospinal fluid
- Administer as intrathecal bolus injection over 1 to 3 minutes

Laboratory Testing and Monitoring to Assess Safety (2.3)
- At baseline and prior to each dose, obtain a platelet count, coagulation laboratory testing, and quantitative spot urine protein testing

DOSAGE FORMS AND STRENGTHS
Injection: 12 mg/5 mL (2.4 mg/mL) in a single-dose vial (3)

CONTRAINDICATIONS
None.

WARNINGS AND PRECAUTIONS
- Thrombocytopenia and Coagulation Abnormalities: Increased risk for bleeding complications; testing required at baseline and before each dose and as clinically needed (5.1, 2.3)
- Renal Toxicity: Quantitative spot urine protein testing required at baseline and prior to each dose (5.2, 2.3)

ADVERSE REACTIONS
The most common adverse reactions that occurred in at least 20% of SPINRAZA-treated patients and occurred at least 5% more frequently than in control patients were:
- lower respiratory infection and constipation in patients with infantile-onset SMA (6.1)
- pyrexia, headache, vomiting, and back pain in patients with later-onset SMA (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Biogen at 1-844-477-4672 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS
Pregnancy: Based on animal data, may cause fetal harm (8.1)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 06/2019

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
  2.1 Dosing Information
  2.2 Important Administration Instructions
  2.3 Laboratory Testing and Monitoring to Assess Safety
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
  5.1 Thrombocytopenia and Coagulation Abnormalities
  5.2 Renal Toxicity
6 ADVERSE REACTIONS
  6.1 Clinical Trials Experience
  6.2 Immunogenicity
  6.3 Postmarketing Experience
8 USE IN SPECIFIC POPULATIONS
  8.1 Pregnancy
  8.2 Lactation
  8.4 Pediatric Use
  8.5 Geriatric Use
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
  12.1 Mechanism of Action
  12.2 Pharmacodynamics
  12.3 Pharmacokinetics
13 NONCLINICAL TOXICOLOGY
  13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
14 CLINICAL STUDIES
  14.1 Infantile-Onset SMA
  14.2 Later-Onset SMA
  14.3 Presymptomatic SMA
16 HOW SUPPLIED/STORAGE AND HANDLING
  16.1 How Supplied
  16.2 Storage and Handling
17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.
FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE
SPINRAZA is indicated for the treatment of spinal muscular atrophy (SMA) in pediatric and adult patients.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Information
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.

2.2 Important Preparation and Administration Instructions
SPINRAZA is for intrathecal use only.

Prepare and use SPINRAZA according to the following steps using aseptic technique. Each vial is intended for single dose only.

Preparation
- Store SPINRAZA in the carton in a refrigerator until time of use.
- Allow the SPINRAZA vial to warm to room temperature (25° C/77° F) prior to administration. Do not use external heat sources.
- Inspect the SPINRAZA vial for particulate matter and discoloration prior to administration. Do not administer SPINRAZA if visible particulates are observed or if the liquid in the vial is discolored. The use of external filters is not required.
- Withdraw 12 mg (5 mL) of SPINRAZA from the single-dose vial into a syringe and discard unused contents of the vial.
- Administer SPINRAZA within 4 hours of removal from vial.

Administration
- Consider sedation as indicated by the clinical condition of the patient.
Consider ultrasound or other imaging techniques to guide intrathecal administration of SPINRAZA, particularly in younger patients.

Prior to administration, remove 5 mL of cerebrospinal fluid.

Administer SPINRAZA as an intrathecal bolus injection over 1 to 3 minutes using a spinal anesthesia needle [see Dosage and Administration (2.1)]. Do not administer SPINRAZA in areas of the skin where there are signs of infection or inflammation [see Adverse Reactions (6.3)].

2.3 Laboratory Testing and Monitoring to Assess Safety

Conduct the following laboratory tests at baseline and prior to each dose of SPINRAZA and as clinically needed [see Warnings and Precautions (5.1, 5.2)]:

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

3 DOSAGE FORMS AND STRENGTHS

Injection: 12 mg/5 mL (2.4 mg/mL) nusinersen as a clear and colorless solution in a single-dose vial.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Thrombocytopenia and Coagulation Abnormalities

Coagulation abnormalities and thrombocytopenia, including acute severe thrombocytopenia, have been observed after administration of some antisense oligonucleotides.

In the sham-controlled studies for patients with infantile-onset and later-onset SMA, 24 of 146 (16%) SPINRAZA-treated patients with high, normal, or unknown platelet count at baseline developed a platelet level below the lower limit of normal, compared to 10 of 72 (14%) sham-controlled patients.

In the sham-controlled study in patients with later-onset SMA (Study 2), two SPINRAZA-treated patients developed platelet counts less than 50,000 cells per microliter, with a lowest level of 10,000 cells per microliter recorded on study day 28.

Because of the risk of thrombocytopenia and coagulation abnormalities from SPINRAZA, patients may be at increased risk of bleeding complications.
Perform a platelet count and coagulation laboratory testing at baseline and prior to each administration of SPINRAZA and as clinically needed.

5.2 Renal Toxicity

Renal toxicity, including potentially fatal glomerulonephritis, has been observed after administration of some antisense oligonucleotides.

SPINRAZA is present in and excreted by the kidney [see Clinical Pharmacology (12.3)]. In the sham-controlled studies for patients with infantile-onset and later-onset SMA, 71 of 123 (58%) of SPINRAZA-treated patients had elevated urine protein, compared to 22 of 65 (34%) sham-controlled patients. Conduct quantitative spot urine protein testing (preferably using a first morning urine specimen) at baseline and prior to each dose of SPINRAZA. For urinary protein concentration greater than 0.2 g/L, consider repeat testing and further evaluation.

6 ADVERSE REACTIONS

The following serious adverse reactions are described in detail in other sections of the labeling:

- Thrombocytopenia and Coagulation Abnormalities [see Warnings and Precautions (5.1)]
- Renal Toxicity [see Warnings and Precautions (5.2)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of SPINRAZA cannot be directly compared to rates in clinical trials of other drugs and may not reflect the rates observed in practice.

The data described below reflect exposure to SPINRAZA in 260 patients (48% male, 80% Caucasian), including 227 exposed for at least 6 months and 181 exposed for at least 1 year. The safety of SPINRAZA was studied in presymptomatic infants with SMA; pediatric patients (approximately 3 days to 16 years of age at first dose) with symptomatic SMA; in a sham-controlled trial in infants with symptomatic SMA (Study 1; n=80 for SPINRAZA, n=41 for control); in a sham-controlled trial in children with symptomatic SMA (Study 2; n=84 for SPINRAZA, n=42 for control); in open-label studies in presymptomatic and symptomatic infants (n=40); and in open-label studies in later onset patients (n=56). In Study 1, 58 patients were exposed for at least 6 months and 28 patients were exposed for at least 12 months. In Study 2, 84 patients were exposed for at least 6 months and 82 patients were exposed for at least 12 months.

Clinical Trial in Infantile-Onset SMA (Study 1)

In Study 1, baseline disease characteristics were largely similar in the SPINRAZA-treated patients and sham-control patients except that SPINRAZA-treated patients at baseline had a higher percentage compared to sham-control patients of paradoxical breathing (89% vs 66%).
pneumonia or respiratory symptoms (35% vs 22%), swallowing or feeding difficulties (51% vs 29%), and requirement for respiratory support (26% vs 15%).

The most common adverse reactions that occurred in at least 20% of SPINRAZA-treated patients and occurred at least 5% more frequently than in control patients 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 Study 1 were infants, adverse reactions that are verbally reported could not be assessed in this study.

Table 1.  Adverse Reactions that Occurred in at Least 5% of SPINRAZA Patients and Occurred at Least 5% More Frequently or At Least 2 Times as Frequently Than in Control Patients with Infantile-Onset SMA (Study 1)

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>SPINRAZA 12 mg(^1)</th>
<th>Sham-Procedure Control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 80</td>
<td>N = 41</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Lower respiratory infection(^2)</td>
<td>55</td>
<td>37</td>
</tr>
<tr>
<td>Constipation</td>
<td>35</td>
<td>22</td>
</tr>
<tr>
<td>Teething</td>
<td>18</td>
<td>7</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>Upper respiratory tract congestion</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>Ear infection</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Flatulence</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Decreased weight</td>
<td>5</td>
<td>2</td>
</tr>
</tbody>
</table>

\(^1\) Loading doses followed by 12 mg (5 mL) once every 4 months
\(^2\) Includes adenovirus infection, bronchiolitis, bronchitis, bronchitis viral, corona virus infection, Influenza, lower respiratory tract infection, lower respiratory tract infection viral, lung infection, parainfluenza virus infection, pneumonia, pneumonia bacterial, pneumonia influenza, pneumonia moraxella, pneumonia parainfluenzae viral, pneumonia pneumococcal, pneumonia pseudomonal, pneumonia respiratory syncytial viral, pneumonia viral, and respiratory syncytial virus bronchiolitis.

In an open-label clinical study in infants with symptomatic SMA, severe hyponatremia was reported in a patient treated with SPINRAZA requiring salt supplementation for 14 months.

Cases of rash were reported in patients treated with SPINRAZA. One patient, 8 months after starting SPINRAZA treatment, developed painless red macular lesions on the forearm, leg, and foot over an 8-week period. The lesions ulcerated and scabbed over within 4 weeks, and resolved
over several months. A second patient developed red macular skin lesions on the cheek and hand ten months after the start of SPINRAZA treatment, which resolved over 3 months. Both cases continued to receive SPINRAZA and had spontaneous resolution of the rash. 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.

Clinical Trial in Later-Onset SMA (Study 2)

In Study 2, baseline disease characteristics were largely similar in the SPINRAZA-treated patients and sham-control patients except for the proportion of SPINRAZA-treated patients who had ever achieved the ability to stand without support (13% vs 29%) or walk with support (24% vs 33%).

The most common adverse reactions that occurred in at least 20% of SPINRAZA-treated patients and occurred at least 5% more frequently than in control patients were pyrexia, headache, vomiting, and back pain.
Table 2. Adverse Reactions that Occurred in at Least 5% of SPINRAZA Patients and Occurred at Least 5% More Frequently or At Least 2 Times as Frequently Than in Control Patients with Later-Onset SMA (Study 2)

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>SPINRAZA 12 mg¹</th>
<th>Sham-Procedure Control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=84</td>
<td>N=42</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>43</td>
<td>36</td>
</tr>
<tr>
<td>Headache</td>
<td>29</td>
<td>7</td>
</tr>
<tr>
<td>Vomiting</td>
<td>29</td>
<td>12</td>
</tr>
<tr>
<td>Back pain</td>
<td>25</td>
<td>0</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Fall</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory tract congestion</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Seasonal allergy</td>
<td>5</td>
<td>2</td>
</tr>
</tbody>
</table>

¹ Loading doses followed by 12 mg (5 mL) once every 6 months

Post-lumbar puncture syndrome has also been observed after administration of SPINRAZA.

6.2 Immunogenicity

As with all oligonucleotides, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to nusinersen in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

The immunogenic response to nusinersen was determined in 249 patients with post-baseline plasma samples evaluated for anti-drug antibodies (ADAs). Sixteen patients (6%) developed treatment-emergent ADAs, of which 3 were transient,13 were considered to be persistent. Persistent was defined as having one positive test followed by another one more than 100 days after the first positive test. In addition, “persistent” is also defined as having one or more positive samples and no sample more than 100 days after the first positive sample. Transient was defined as having one or more positive results and not confirmed to be persistent. There are insufficient data to evaluate an effect of ADAs on clinical response, adverse events, or the pharmacokinetic profile of nusinersen.
6.3 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of SPINRAZA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Serious infections associated with lumbar puncture, such as meningitis, have been observed. Hydrocephalus, aseptic meningitis, and hypersensitivity reactions (e.g. angioedema, urticaria, rash) have also been reported.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate data on the developmental risk associated with the use of SPINRAZA in pregnant women. When nusinersen was administered by subcutaneous injection to mice throughout pregnancy and lactation, developmental toxicity (long-term neurobehavioral impairment) was observed at all doses tested (see Data). In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively. The background risk of major birth defects and miscarriage for the indicated population is unknown.

Data

Animal Data

When nusinersen (0, 3, 10, or 25 mg/kg) was administered subcutaneously to male and female mice every other day prior to and during mating and continuing in females throughout organogenesis, no adverse effects on embryofetal development were observed. Subcutaneous administration of nusinersen (0, 6, 12.6, or 25 mg/kg) to pregnant rabbits every other day throughout organogenesis produced no evidence of embryofetal developmental toxicity.

When nusinersen (1.4, 5.8, or 17.2 mg/kg) was administered to pregnant female mice by subcutaneous injection every other day throughout organogenesis and continuing once every six days throughout the lactation period, adverse neurobehavioral effects (alterations in locomotor activity, learning and memory deficits) were observed when offspring were tested after weaning or as adults. A no-effect level for neurobehavioral impairment was not established.
8.2 Lactation

Risk Summary

There are no data on the presence of nusinersen in human milk, the effects on the breastfed infant, or the effects of the drug on milk production. Nusinersen was detected in the milk of lactating mice when administered by subcutaneous injection. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for SPINRAZA and any potential adverse effects on the breastfed infant from SPINRAZA or from the underlying maternal condition.

8.4 Pediatric Use

The safety and effectiveness of SPINRAZA in pediatric patients from newborn to 17 years have been established [see Clinical Studies (14.1)].

Juvenile Animal Toxicity Data

In intrathecal toxicity studies in juvenile monkeys, administration of nusinersen (0, 0.3, 1, or 3 mg/dose for 14 weeks and 0, 0.3, 1, or 4 mg/dose for 53 weeks) resulted in brain histopathology (neuronal vacuolation and necrosis/cellular debris in the hippocampus) at the mid and high doses and acute, transient deficits in lower spinal reflexes at the high dose in each study. In addition, possible neurobehavioral deficits were observed on a learning and memory test at the high dose in the 53-week monkey study. The no-effect dose for neurohistopathology in monkeys (0.3 mg/dose) is approximately equivalent to the human dose when calculated on a yearly basis and corrected for the species difference in CSF volume.

8.5 Geriatric Use

Clinical studies of SPINRAZA did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

11 DESCRIPTION

Nusinersen is a modified antisense oligonucleotide, where the 2’-hydroxy groups of the ribofuranosyl rings are replaced with 2’-O-2-methoxyethyl groups and the phosphate linkages are replaced with phosphorothioate linkages. Nusinersen binds to a specific sequence in the intron downstream of exon 7 of the SMN2 transcript. The structural formula is:
SPINRAZA is supplied as a sterile, preservative-free, colorless solution for intrathecal use in a single-dose glass vial. Each 1 mL solution contains 2.4 mg of nusinersen (equivalent to 2.53 mg of nusinersen sodium salt). Each 1 mL also contains calcium chloride dihydrate (0.21 mg) USP, magnesium chloride hexahydrate (0.16 mg) USP, potassium chloride (0.22 mg) USP, sodium chloride (8.77 mg) USP, sodium phosphate dibasic anhydrous (0.10 mg) USP, sodium phosphate monobasic dihydrate (0.05 mg) USP, and Water for Injection USP. The product may contain hydrochloric acid or sodium hydroxide to adjust pH. The pH is ~7.2.

The molecular formula of SPINRAZA is C\textsubscript{234}H\textsubscript{323}N\textsubscript{61}O\textsubscript{128}P\textsubscript{17}S\textsubscript{17}Na\textsubscript{17} and the molecular weight is 7501.0 daltons.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

SPINRAZA is an antisense oligonucleotide (ASO) designed to treat SMA caused by mutations in chromosome 5q that lead to SMN protein deficiency. Using in vitro assays and studies in transgenic animal models of SMA, SPINRAZA was shown to increase exon 7 inclusion in SMN2 messenger ribonucleic acid (mRNA) transcripts and production of full-length SMN protein.

12.2 Pharmacodynamics

Autopsy samples from patients (n=3) had higher levels of SMN2 messenger ribonucleic acid (mRNA) containing exon 7 in the thoracic spinal cord compared to untreated SMA infants.

Cardiac Electrophysiology
Across the sham-controlled studies in 247 patients with spinal muscular atrophy who received either SPINRAZA or sham-control, QTcF values >500 ms and change from baseline values >60 ms were observed in 4 (2.4%) patients receiving SPINRAZA. Compared to the sham-control, there was no increase in the incidence of cardiac adverse reactions associated with delayed ventricular repolarization in patients treated with SPINRAZA.

### 12.3 Pharmacokinetics

**Absorption**

Intrathecal injection of SPINRAZA into the cerebrospinal fluid (CSF) allows nusinersen to be distributed from the CSF to the target central nervous system (CNS) tissues. Following intrathecal administration, trough plasma concentrations of nusinersen were relatively low, compared to the trough CSF concentration. Median plasma $T_{max}$ values ranged from 1.7 to 6.0 hours. Mean plasma $C_{max}$ and AUC values increased approximately dose-proportionally up to a dose of 12 mg.

**Distribution**

Autopsy data from patients ($n=3$) showed that SPINRAZA administered intrathecally was distributed within the CNS and peripheral tissues, such as skeletal muscle, liver, and kidney.

**Elimination**

**Metabolism**

Nusinersen is metabolized via exonuclease (3’- and 5’)-mediated hydrolysis and is not a substrate for, or inhibitor or inducer of CYP450 enzymes.

**Excretion**

The mean terminal elimination half-life is estimated to be 135 to 177 days in CSF, and 63 to 87 days in plasma. The primary route of elimination is likely by urinary excretion for nusinersen and its chain-shortened metabolites. At 24 hours, only 0.5% of the administered dose was recovered in the urine.

### 13 NONCLINICAL TOXICOLOGY

#### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

**Carcinogenesis**

Long-term studies in animals to evaluate the carcinogenic potential of nusinersen have not been performed.

**Mutagenesis**

Nusinersen demonstrated no evidence of genotoxicity in in vitro (Ames and chromosomal aberration in CHO cells) and in vivo (mouse micronucleus) assays.

**Impairment of Fertility**
When nusinersen (0, 3, 10, or 25 mg/kg) was administered by subcutaneous injection to mice every other day prior to and during mating and continuing in females throughout organogenesis, no adverse effects on male or female fertility were observed.

14 CLINICAL STUDIES

The efficacy of SPINRAZA was demonstrated in two double-blind, sham-procedure controlled clinical trials in symptomatic infantile-onset and later-onset SMA patients (Study 1 and Study 2) and was supported by open-label clinical trials conducted in presymptomatic and symptomatic SMA patients. The overall findings from these trials support the effectiveness of SPINRAZA across the range of SMA patients, and appear to support the early initiation of treatment with SPINRAZA.

14.1 Infantile-Onset SMA

Study 1 was a multicenter, randomized, double-blind, sham-procedure controlled study in 121 symptomatic infants ≤ 7 months of age at the time of first dose, diagnosed with SMA (symptom onset before 6 months of age). Patients were randomized 2:1 to receive either 12 mg SPINRAZA or sham injection as a series of loading doses administered intrathecally followed by maintenance doses administered every 4 months. Patients in this study were deemed most likely to develop Type 1 SMA.

A planned interim efficacy analysis was conducted based on patients who died, withdrew, or completed at least 183 days of treatment. Of the 82 patients included in the interim analysis (52 patients in the SPINRAZA-treated group and 30 in the sham-control group), 44% were male, 87% were Caucasian, 2% were Black, and 4% were Asian. Age at first treatment ranged from 30 to 262 days (median 181). Length of treatment ranged from 6 to 442 days (median 261 days). Baseline demographics were balanced between the SPINRAZA and control groups with the exception of age at first treatment (median age 175 vs. 206 days, respectively). The SPINRAZA and control groups were balanced with respect to gestational age, birth weight, disease duration, and SMN2 copy number. Median disease duration was 14 weeks. There was some imbalance in age at symptom onset with 88% of subjects in the SPINRAZA group and 77% in the control group experiencing symptoms within the first 12 weeks of life.

The primary endpoint assessed at the time of 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). This endpoint evaluates seven different areas of motor milestone development, with a maximum score between 2-4 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 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. Of the 82 patients who were eligible for the interim analysis, a statistically significantly greater percentage of patients achieved the
definition of a motor milestone responder in the SPINRAZA group (40%) compared to the sham-control group (0%). Results from the final analysis were consistent with those from the interim analysis (Table 3). Fifty-one percent of patients in the SPINRAZA group achieved the definition of a motor milestone responder compared to 0% of patients in the sham-control group. Figure 1 is a descriptive display of the distribution of net change from baseline in the total motor milestone score for Section 2 of the HINE for patients in the final efficacy set who did not die or withdraw from the study.

The primary endpoint assessed at the final analysis was time to death or permanent ventilation (≥16 hours ventilation/day continuously for > 21 days in the absence of an acute reversible event or tracheostomy). Statistically significant effects on event-free survival and overall survival were observed in patients in the SPINRAZA group compared to those in the sham-control group (Table 4). A 47% reduction in the risk of death or permanent ventilation was observed in the SPINRAZA group (p=0.005) (Figure 2). Median time to death or permanent ventilation was not reached in SPINRAZA group and was 22.6 weeks in the sham-control group. A statistically significant 63% reduction in the risk of death was also observed (p=0.004).

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 CHOP-INTEND results are displayed in Table 3.

Table 3. Motor Milestone Response and CHOP-INTEND Results of the Final Analysis of Patients with Infantile-Onset SMA (Study 1)

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>SPINRAZA-treated Patients (n=73)</th>
<th>Sham-control Patients (n=37)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Motor function</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Motor milestones</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proportion achieving pre-defined motor milestone responder criteria (HINE section 2)²,³</td>
<td>37 (51%) P&lt;0.0001</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>CHOP-INTEND¹</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proportion achieving a 4-point improvement</td>
<td>52 (71%) p&lt;0.0001</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Proportion achieving a 4-point worsening⁴</td>
<td>2 (3%)</td>
<td>17 (46%)</td>
</tr>
</tbody>
</table>

¹At the final analysis, CHOP-INTEND and motor milestone analyses were conducted using the Efficacy Set (SPINRAZA n=73; Sham-control n=37).
²Assessed at the later of Day 183, Day 302, and Day 394 Study Visit
³According to HINE section 2: ≥2 point increase [or maximal score] in ability to kick, OR ≥1 point increase in the motor milestones of head control, rolling, sitting, crawling, standing or walking, AND improvement in more categories of motor milestones than worsening), defined as a responder for this primary analysis.
⁴Not statistically controlled for multiple comparisons
Table 4. Survival Results of Patients with Infantile-Onset SMA (Study 1)

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>SPINRAZA-treated Patients (n=80)</th>
<th>Sham-control Patients (n=41)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survival</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Event-free survival¹</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients who died</td>
<td>31 (39%)</td>
<td>28 (68%)</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.53 (0.32-0.89)</td>
<td></td>
</tr>
<tr>
<td>p-value²</td>
<td>p=0.005</td>
<td></td>
</tr>
<tr>
<td>Overall survival¹</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients who died</td>
<td>13 (16%)</td>
<td>16 (39%)</td>
</tr>
<tr>
<td>Hazard Ratio (95% CI)</td>
<td>0.37 (0.18-0.77)</td>
<td></td>
</tr>
<tr>
<td>p-value²</td>
<td>p=0.004</td>
<td></td>
</tr>
</tbody>
</table>

¹At the final analysis, event-free survival and overall survival were assessed using the Intent to Treat population (ITT SPINRAZA n=80; Sham-control n=41).
²Based on log-rank test stratified by disease duration

Figure 1. Percent of Patients Who Died and Net Change from Baseline in Total Motor Milestone Score (HINE) Among Patients Alive in the Final Efficacy Set of Study 1 *

*For subjects who were alive and ongoing in the study, the change in total motor milestone score was calculated at the later of Day 183, Day 302, or Day 394.
14.2 Later-Onset SMA

Study 2 was a multicenter, randomized, double-blind, sham-procedure controlled study in 126 symptomatic children with later-onset SMA (symptom onset after 6 months of age). Patients were randomized 2:1 to either SPINRAZA 12 mg or sham injection as a series of loading doses administered intrathecally followed by maintenance doses administered every 6 months.

The median age at screening was 3 years (range 2-9 years), and the median age of onset of clinical signs and symptoms of SMA was 11 months (range 6-20 months). Of the 126 patients included in the study, 47% were male, 75% were Caucasian, 2% were Black, and 18% were Asian. Length of treatment ranged from 324 to 482 days (median 450 days). At baseline, patients had a mean Hammersmith Functional Motor Scale – Expanded (HFMSE) score of 21.6, all had achieved independent sitting, and no patients had achieved independent walking. Patients in this study were deemed most likely to develop Type 2 or 3 SMA.

The primary endpoint assessed was the change from baseline score at Month 15 on the HFMSE. The HFMSE evaluates motor function in patients with SMA who have limited ambulation, comprising of 33 scored activities that give objective information on motor ability and clinical progression, such as the ability to sit unassisted, stand, or walk. Each item is scored from 0-2, with a maximum total score of 66. Higher scores indicate better motor function. The primary
analysis was conducted in the Intent to Treat (ITT) population, which included all subjects who were randomized and received at least 1 dose of SPINRAZA or at least one sham procedure. At the final analysis, a statistically significant improvement in HFMSE scores from baseline to Month 15 was observed in the SPINRAZA-treated group compared to the sham-control group (Table 5).

**Table 5: HFMSE Results in Patients with Later-Onset SMA (Study 2)**

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>SPINRAZA-treated Patients (n=84)</th>
<th>Sham-control Patients (n=42)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HFMSE score</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change from baseline in total HFMSE score at 15 months$^{1,2,3}$</td>
<td>3.9 (95% CI: 3.0, 4.9) p=0.0000001</td>
<td>-1.0 (95% CI: -2.5, 0.5)</td>
</tr>
<tr>
<td>Proportion of patients who achieved at least a 3-point improvement from baseline to Month 15$^1$</td>
<td>56.8% (95% CI: 45.6, 68.1) p=0.0006$^4$</td>
<td>26.3% (95% CI: 12.4, 40.2)</td>
</tr>
</tbody>
</table>

$^1$Assessed using the Intent to Treat population who received at least one dose of SPINRAZA or at least one sham procedure (SPINRAZA n=84; Sham-control n=42); data for patients without a Month 15 visit were imputed using the multiple imputation method

$^2$Least squares mean

$^3$Negative value indicates worsening, positive value indicates improvement.

$^4$Based on logistic regression with treatment effect and adjustment for each subject's age at screening and HFMSE score at baseline
Figure 3. Mean Change from Baseline in HFMSE Score Over Time in the Intent to Treat Set1,2 (Study 2)

1Data for patients without a Month 15 visit were imputed using the multiple imputation method
2Error bars denote +/- standard error

14.3 Presymptomatic SMA

The results of the sham-controlled trial in infantile-onset and later-onset SMA patients were supported by an open-label uncontrolled trial conducted in presymptomatic SMA patients, who ranged in age from 3 days to 42 days at the time of first dose. Patients received 12 mg SPINRAZA as a series of loading doses administered intrathecally followed by maintenance doses administered every 4 months.

Some patients receiving SPINRAZA before the onset of SMA symptoms survived without requiring permanent ventilation beyond what would be expected based on their SMN2 copy number, and some patients also achieved age-appropriate growth and developmental motor milestones such as the ability to sit unassisted, stand, or walk.
16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

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. The NDC is 64406-058-01.

16.2 Storage and Handling

Store in a refrigerator between 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Do not freeze.

SPINRAZA should be protected from light and kept in the original carton until time of use. If no refrigeration is available, SPINRAZA may be stored in its original carton, protected from light at or below 30°C (86°F) for up to 14 days.

Prior to administration, unopened vials of SPINRAZA can be removed from and returned to the refrigerator, if necessary. If removed from the original carton, the total combined time out of refrigeration should not exceed 30 hours at a temperature that does not exceed 25°C (77°F).

17 PATIENT COUNSELING INFORMATION

Thrombocytopenia and Coagulation Abnormalities
Inform patients and caregivers that SPINRAZA could increase the risk of bleeding. Inform patients and caregivers of the importance of obtaining blood laboratory testing at baseline and prior to each dose to monitor for signs of increased potential for bleeding. Instruct patients and caregivers to seek medical attention if unexpected bleeding occurs [see Warnings and Precautions (5.1)].

Renal Toxicity
Inform patients and caregivers that SPINRAZA could cause renal toxicity. Inform patients and caregivers of the importance of obtaining urine testing at baseline and prior to each dose to monitor for signs of potential renal toxicity [see Warnings and Precautions (5.2)].

49655-07

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Biogen
Cambridge, MA 02142
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