A GUIDE TO SPINRAZA REIMBURSEMENT

IMPORTANT INFORMATION TO HELP NAVIGATE THE ACCESS AND REIMBURSEMENT PROCESS

Please see full Prescribing Information for additional Important Safety Information.

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INTRODUCTION

WELCOME

We are excited to share with you the approval of SPINRAZA™ (nusinersen), the first and only 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 December 23, 2016 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° support provides certain services that address nonmedical barriers to access. These include logistical assistance, product education, insurance benefits investigations, and financial assistance. A complete list of the SMA360° offerings can be found at www.SPINRAZA-hcp.com/support.

With a highly variable disease like SMA, needs may vary as well. Your patients or their caregivers might 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.

Your patients’ SMA360° team is made up of some important people: their Family Access Manager (FAM) and their SMA Support Coordinator.

Additional information about the services provided by SMA360° and are included in this guide.

SMA360° services from Biogen are available only to those who have been prescribed SPINRAZA. SMA360° is available only in the US.

INDICATION

SPINRAZA 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. Perform a platelet count and coagulation laboratory testing at baseline and prior to each administration of SPINRAZA and as clinically needed.

In a clinical study, 11% of SPINRAZA-treated patients with normal or above normal platelet levels at baseline developed a platelet level below the lower limit of normal compared to zero sham-procedure control patients. No patient had a platelet count <50,000 cells per mcL and no patient developed a sustained low platelet count despite continued drug exposure.

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No elevations in serum creatinine or cystatin C were observed in studies with SPINRAZA. 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 >0.2 g/L, consider repeat testing and further evaluation.

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Overview of the Reimbursement Process for SPINRAZA™ (nusinersen)
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.

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.

IMPORTANT SAFETY INFORMATION (continued)

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A SPINRAZA care plan will help guide the Benefit Investigation

**A.** Develop a patient-specific SPINRAZA care plan based on the individual patient needs, such as:
- Institution or practice where SPINRAZA will be administered (i.e., site name)
- Setting of care for SPINRAZA administration and related post-injection observation (e.g., outpatient hospital, ambulatory surgical center (ASC), physician office, observational stay, hospital inpatient)
- Ancillary services to be used for SPINRAZA administration (e.g., sedation, ultrasound, fluoroscopy)
- Professional providers to be involved in SPINRAZA administration (e.g., anesthesiologist, neuroradiologist, neurologist)

**B.** Understand how SPINRAZA will be obtained in alignment with your practice or facility procurement process

**C.** Confirm the care plan with the patient/caregiver and discuss the treatment process to help set appropriate expectations:
- Expected timelines before treatment can be initiated
- Current payer coverage situation and any anticipated changes
- Possible financial needs

**D.** Introduce SMA360° support services, which are available to help the patient’s family understand and navigate the treatment process

**IMPORTANT SAFETY INFORMATION** (continued)

The most common adverse reactions that occurred in the controlled study in at least 20% of SPINRAZA-treated patients and occurred at least 5% more frequently than in control patients were upper respiratory infection (39% vs 34%), lower respiratory infection (43% vs 29%), and constipation (30% vs 22%). Serious adverse reactions of atelectasis were more frequent in SPINRAZA-treated patients (14%) than in control patients (5%). Because patients in the controlled study were infants, adverse reactions that are verbally reported could not be assessed in this study. In the open-label studies, the most common adverse events in later onset patients were headache (50%), back pain (41%) and post lumbar puncture syndrome (41%).

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Financial assistance and insurance counseling

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)

*For additional details, please refer to pages 31-33 of this guide.*

*Other programs may also be available for your patients.*

**IMPORTANT SAFETY INFORMATION (continued)**

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Schedule patient visit for SPINRAZA administration and make appropriate patient coordination arrangements

A. Considerations
- Clinic visit for pre-procedure exam, if needed
- Intrathecal injection procedure scheduled with appropriate department
- Notify hospital outpatient admission department of prior authorization approval and treatment date
- Notify correct pharmacy department of prior authorization approval and treatment date
- Assist family with local overnight accommodations, if needed

The SMA360° team will contact the enrolled patient’s family regarding treatment logistics for the SPINRAZA administration visit

B. The SMA360° team coordinates logistics with the patient’s family and the site of care in preparation for the SPINRAZA administration visit

CuraScript Specialty Distributor (SD)/Accredo Specialty Pharmacy (SP) is the exclusive authorized provider of SPINRAZA

C. Order SPINRAZA from CuraScript SD/Accredo SP for delivery before the scheduled patient visit:
- The ordering process for SPINRAZA is through your facility’s pharmacy or procurement department, as it would be for any other treatment

For additional details, please refer to page 35 of this guide.

IMPORTANT SAFETY INFORMATION (continued)
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Developing a SPINRAZA™ (nusinersen) Care Plan
AN INDIVIDUALIZED CARE PLAN WILL HELP GUIDE THE BENEFIT INVESTIGATION

When an HCP in your practice or facility decides to initiate treatment with SPINRAZA for a clinically appropriate patient, one of the first critical steps is to develop a detailed care plan that can guide the Benefit Investigation. As every patient with SMA is unique, a SPINRAZA care plan will need to be individualized based on the specific patient’s needs. The Benefit Investigation process will help determine insurance coverage and potential patient OOP costs for the unique aspects of a patient-specific SPINRAZA care plan.

One of the key components of a care plan is the site of care for SPINRAZA administration, because it may have important implications for payer coverage and patient OOP costs.

Outpatient hospital-based facility
Freestanding ASC
Physician office
Inpatient hospital facility

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

IMPORTANT SAFETY INFORMATION (continued)
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SITE-OF-CARE CONSIDERATIONS

Several factors can influence the decision to administer SPINRAZA in a particular site of care. In order to ensure that the selected site of care can appropriately address patient needs, it is important that these factors are considered by the key stakeholders involved in patient care, including clinicians, administrators, and the patient’s family.

KEY SITE-OF-CARE CONSIDERATIONS

**Administration procedure and related ancillary services**

Depending on the patient’s age and clinical condition, some patients may require ancillary services in order to administer SPINRAZA.

**Considerations**

- The site has the appropriate clinical specialists who may need to be involved in the administration of SPINRAZA (e.g., neurologist, anesthesiologist, radiologist) based on the individual patient’s needs.
- The site is prepared with the necessary equipment that may be needed for ancillary services (e.g., sedation, lumbar puncture, ultrasound, fluoroscopy).

SPINRAZA is administered intrathecally by, or under the direction of, HCPs with experience performing lumbar punctures. There may be a need for ancillary services, including sedation or the use of ultrasound or other imaging techniques.

**IMPORTANT SAFETY INFORMATION (continued)**

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After SPINRAZA is administered in an outpatient setting, some patients may require additional monitoring and/or management in a hospital facility. For certain patients, providers may also consider administering SPINRAZA in a hospital inpatient setting.

**Considerations**
- If additional postinjection monitoring is required, the site can accommodate or transfer the patient for outpatient observation
- If clinically necessary, the site can admit or transfer the patient for an inpatient stay

**Payer reimbursement methodology for facility and professional services may vary substantially across sites of care**

**Considerations**
- The facility and/or professional services may be subject to some form of global payment rules or prospectively set reimbursement rates (e.g., global surgery payment, diagnosis-related groups (DRGs)-based payment)
- The payment for SPINRAZA may be separate or may be bundled within a prospectively set rate (e.g., DRG-based 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.

During an outpatient observation stay, a patient may occupy any bed in the hospital; however, for billing purposes, he or she will have an outpatient status, which has important implications for hospital reimbursement and patient OOP costs.

An outpatient observation stay is typically completed within 24 to 48 hours, at which point the patient can either be admitted for an inpatient stay or discharged from the hospital. It is important to note that payers may cover different lengths of outpatient observation stays. For instance, while Medicaid may allow up to 48 hours for an outpatient observation stay, some private commercial payers may cover only 23 hours in outpatient observation. Please verify the requirements for an outpatient observation stay with the patient’s insurance carrier(s).

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**KEY SITE-OF-CARE CONSIDERATIONS (cont’d)**

**Patient eligibility for financial assistance**

Financial assistance programs may vary by site of care

**Considerations**

- The patient may potentially require financial assistance
- There may be site-of-care restrictions for the available financial assistance programs:

**Patient travel needs**

Traveling can be challenging for patients with SMA and their families. Different levels of accommodation and logistical support might be needed, depending on the distance between the site of care and the patient’s home

**Considerations**

- The patient’s family may have logistical limitations or preferences for the potential site of care options

### Site-of-care 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 site of care does not limit the patient’s eligibility for Biogen financial assistance programs. Your patient’s FAM from Biogen will work with each patient’s family to review and coordinate the financial support options to help pay for the expenses at the site of care; options may include:

- **$0 Procedure Copay Program from Biogen**: Covers the out-of-pocket cost of the administration of SPINRAZA for eligible patients

- **Third-Party Funding Assistance**: Financial assistance with premiums, copays, and other needs for eligible patients

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CARE PLAN 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 (performed as a separate procedure)
  - 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

☐ Select the setting and the site of care 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

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

☐ Document the administration plan for the dosing schedule
  - Dates of loading doses
  - Dates of maintenance doses (if applicable)

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CARE PLAN CHECKLIST (cont’d)

 Coordinate with the patient and his or her caregiver to confirm the care plan 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 them in completing the patient portion, and review caregiver consent (see the Appendix on page 56 of this guide 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
- If signed consent is provided, advise the patient’s family that a FAM from Biogen will assist them in coordinating the logistics of treatment, such as insurance and financial considerations, if needed

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Investigating Benefits and Obtaining Authorization
INVESTIGATING BENEFITS AND OBTAINING AUTHORIZATION

A Benefit 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 the individual care plan.

BEGINNING YOUR BENEFIT INVESTIGATION

A Benefit 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 site of care. For SPINRAZA, there may be patients who travel to a site of care for administration 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 Benefit 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 are basic patient and provider considerations that your practice or facility will need to gather to initiate the Benefit Investigation process.

BASIC PATIENT INFORMATION

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

Insurance information
- Policy holder 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)

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

EPO=exclusive provider organization; HMO=health maintenance organization; NPI=National Provider Identifier; POS=point of service (plan); PPO=preferred provider organization.

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BASIC COVERAGE INFORMATION

Contact the payer to gather the following information.

- **Coverage**
  - [ ] Covered
  - [ ] Prior authorization required
  - [ ] Quantity

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

KEEPING ACCURATE RECORDS OF A BENEFIT 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 Benefit 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

BENEFIT INVESTIGATION CONSIDERATIONS

When a new drug is approved by the FDA and made available by manufacturers, payers may not have coverage policies in place. It may take several months for a new product to be evaluated by a payer and for a coverage policy to be determined. Until a payer conducts a formal coverage determination for a new product, coverage may be granted on a case-by-case basis. During that time, providers will likely need to complete additional requirements, such as precertification/prior authorization or medical exception, in order to gain coverage of the drug, its administration services, and, possibly, the site of care.

During the Benefit Investigation, it is important to determine various specific payer coverage rules and requirements that can impact how patients can access SPINRAZA. The list of key considerations on the next page can serve as a guide for conducting a thorough Benefit Investigation.

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EXAMPLES OF KEY BENEFIT INVESTIGATION CONSIDERATIONS (cont’d)

Some patients who receive SPINRAZA may face restrictions from their commercial and/or Medicaid payers because the provider and/or the service facility is out of network or out of state. It is important to recognize that, for those instances, waivers or exceptions can be granted on the grounds of medical necessity

- Verify the state and/or network participation status for the physician(s) and/or facility involved in the administration of SPINRAZA
- Investigate and record the patient OOP cost implications for out-of-state and/or out-of-network providers
- Find out if there is an exception process for patients seeking care out of state and/or out of network

There may be cases where your patient has multiple payers that provide benefit coverage, such as a commercial health plan and Medicaid.

- In the case of multiple payers, it is important to establish during the Benefit Investigation which payer is first, which is secondary, and which is tertiary, if needed
- Once you have established the order of benefits, follow the instructions from each payer regarding coordination of benefits for reimbursement/payment methodology

Potential provider network restrictions

Each payer may have a network of participating providers who have agreed to provide healthcare services to its members under specific contracted terms. As a result, patients may be restricted or incentivized to seek care from in-network, or preferred, providers. For example, for patients with private commercial insurance, services provided by out-of-network, or nonpreferred, providers may be associated with higher OOP costs or might not be covered at all. For Medicaid beneficiaries, coverage is generally limited to participating providers in the specific state. Furthermore, individuals enrolled in Medicaid Managed Care might only be able to seek care from in-network providers within their state. However, coverage exceptions can be granted as long as medical necessity can be established, especially if there are no in-network providers with the required expertise.

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EXAMPLES OF KEY BENEFIT INVESTIGATION CONSIDERATIONS (cont’d)

**Coding and claims submission details**

Specific coding and billing requirements may vary by payer, particularly for claims with a miscellaneous J-code

- Find out if additional information is required for claims with a miscellaneous J-code and where to include it on the claim
- Clarify the requirements for reporting an NDC number in a medical claim

**Patient financial responsibility**

Patient OOP costs may vary based on the specific benefit design, site of care, 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 BENEFIT INVESTIGATION

SMA360° will also investigate the insurance benefits in order to help the patient and/or their 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 Benefit Investigation conducted by your practice or facility.

Remember to re-verify your patient’s benefits prior to each dose of SPINRAZA, as the insurance coverage may have changed since the patient’s last procedure.

IMPORTANT SAFETY INFORMATION (continued)

The most common adverse reactions that occurred in the controlled study in at least 20% of SPINRAZA-treated patients and occurred at least 5% more frequently than in control patients were upper respiratory infection (39% vs 34%), lower respiratory infection (43% vs 29%), and constipation (30% vs 22%). Serious adverse reactions of atelectasis were more frequent in SPINRAZA-treated patients (14%) than in control patients (5%). Because patients in the controlled study were infants, adverse reactions that are verbally reported could not be assessed in this study. In the open-label studies, the most common adverse events in later onset patients were headache (50%), back pain (41%) and post lumbar puncture syndrome (41%).

Please see following pages for additional Important Safety Information.

Confidential and proprietary to Biogen.
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. Perform a platelet count and coagulation laboratory testing at baseline and prior to each administration of SPINRAZA and as clinically needed.

In a clinical study, 11% of SPINRAZA-treated patients with normal or above normal platelet levels at baseline developed a platelet level below the lower limit of normal compared to zero sham-procedure control patients. No patient had a platelet count <50,000 cells per mcL and no patient developed a sustained low platelet count despite continued drug exposure.

Please see following pages for additional Important Safety Information.

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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 a clinical study, 33% of SPINRAZA-treated patients had elevated urine protein, compared to 20% of sham-control patients. In a group of later-onset SMA patients, 69% had elevated urine protein.

No elevations in serum creatinine or cystatin C were observed in studies with SPINRAZA. 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 >0.2 g/L, consider repeat testing and further evaluation.

Please see following pages for additional Important Safety Information.

Confidential and proprietary to Biogen.
DEMONSTRATING MEDICAL NECESSITY

It is likely that your practice or facility will need to demonstrate to payers that there is a medical necessity for your patient to receive SPINRAZA. As noted in the previous section, a preauthorization/prior authorization request is one area in which your practice or facility may need to address the medical necessity of SPINRAZA for your patients. In addition, there are other situations when it may be necessary to demonstrate medical necessity, such as requesting a medical exception based on the payer’s policy coverage criteria or out-of-network/out-of-state restrictions.

The following are situations in which your practice or facility may need to demonstrate medical necessity for SPINRAZA. 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 57 for a sample of a letter of medical necessity).

EXAMPLES OF SITUATIONS THAT MAY REQUIRE MEDICAL NECESSITY FOR SPINRAZA AND KEY AREAS TO ADDRESS

The payer requires that a preauthorization/prior authorization 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, duration of symptoms, and current supportive care management

The payer reviewed your request for a preauthorization/prior authorization 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 to determine the process for such an exception (ie, 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 patients

IMPORTANT SAFETY INFORMATION (continued)

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.

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EXAMPLES OF SITUATIONS THAT MAY REQUIRE MEDICAL NECESSITY FOR SPINRAZA AND KEY AREAS TO ADDRESS (cont’d)

Medical exception based on policy

The payer has a policy for treatment and administration services for SPINRAZA, and your patient does not meet the requirements; however the physician feels that the treatment is medically necessary

- Point out that the patient requires a medical exception because of reasons indicated by the prescribing physician that demonstrate 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
  - Other relevant aspects of patient history

Exception based on site-of-care restrictions

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 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 patient to a new provider unfamiliar with the patient 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 is no other specialized facilities in their network and/or state
  - Areas of medical specialization and years of experience treating patients with SMA

APPEALING A DENIAL

If your preauthorization/prior authorization or medical exception request for SPINRAZA is denied, you can appeal. Appeals should follow the individual payer’s requirement and include additional information that emphasizes the medical necessity of SPINRAZA for your patient. If your appeal is denied again, there are other courses of action, such as an independent external review. Your Biogen representative can provide information about your state requirements in this area.

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

PATIENT COST-SHARING STRUCTURE CONSIDERATIONS

During the Benefit 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 healthcare providers, or services that are not covered by the plan.

In addition to the Benefit 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.

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. Perform a platelet count and coagulation laboratory testing at baseline and prior to each administration of SPINRAZA and as clinically needed.

In a clinical study, 11% of SPINRAZA-treated patients with normal or above normal platelet levels at baseline developed a platelet level below the lower limit of normal compared to zero sham-procedure control patients. No patient had a platelet count <50,000 cells per mcL and no patient developed a sustained low platelet count despite continued drug exposure.

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No elevations in serum creatinine or cystatin C were observed in studies with SPINRAZA. 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 >0.2 g/L, consider repeat testing and further evaluation.

Please see following pages for additional Important Safety Information.
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 Benefit 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. Fax an Explanation of Benefits (EOB) to Biogen
   - Fax an EOB with the patient’s financial responsibility for SPINRAZA to Biogen at 1-888-656-4343 after each administration.
   - Your practice or facility will receive an instructional letter with steps to complete for reimbursement. The claim form and EOB is then faxed 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 #.

IMPORTANT SAFETY INFORMATION (continued)

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.

Please see following pages for additional Important Safety Information.

Confidential and proprietary to Biogen.
INITIATING THE $0 PROCEDURE 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 the administration procedure that is associated with SPINRAZA, but it does not cover the cost of the drug. After conducting a Benefit 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 Procedure Copay Program for every administration of SPINRAZA. 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 is also available by calling 1-844-4SPINRAZA (1-844-477-4672)

2. **Fax an EOB to Biogen**
   Fax an EOB with the patient’s financial responsibility for the procedure associated with the administration of SPINRAZA to Biogen at 1-888-656-4343 after each administration
   - Your practice or facility will receive an instructional letter with steps to complete for reimbursement. The claim form and EOB is then faxed 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 #

The eligibility criteria differ for the $0 Procedure Copay Program and the $0 Drug Copay Program. For more information, consult with your Biogen representative.

IMPORTANT SAFETY INFORMATION (continued)
The most common adverse reactions that occurred in the controlled study in at least 20% of SPINRAZA-treated patients and occurred at least 5% more frequently than in control patients were upper respiratory infection (39% vs 34%), lower respiratory infection (43% vs 29%), and constipation (30% vs 22%). Serious adverse reactions of atelectasis were more frequent in SPINRAZA-treated patients (14%) than in control patients (5%). Because patients in the controlled study were infants, adverse reactions that are verbally reported could not be assessed in this study. In the open-label studies, the most common adverse events in later onset patients were headache (50%), back pain (41%) and post lumbar puncture syndrome (41%).

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Confidential and proprietary to Biogen.
Ordering
SPINRAZA™ (nusinersen)
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/Accredo Specialty Pharmacy is the exclusive authorized provider of SPINRAZA. Ordering SPINRAZA is done as any other product that is administered at your site of care, whether it is an outpatient hospital-based facility, physician office, freestanding ASC, or inpatient hospital facility. SPINRAZA can be ordered directly through a specialty distributor, CuraScript SD, or from Accredo Specialty Pharmacy. 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
  - Benefit 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 the authorized distributor, CuraScript SD/Accredo Specialty Pharmacy
  - Follow the standard process for placing a prescription drug order in your practice or facility
    - The SPINRAZA Start Form is not a prescription or an order, therefore you will need to follow your standard process to place the order
  - Your pharmacy or procurement department will need to submit the order form to CuraScript SD/Accredo Specialty Pharmacy
    - 1-855-778-1510 (phone)
    - 1-866-579-4655 (fax)

- Coordinate SPINRAZA shipment delivery with the scheduled patient treatment visit
  - CuraScript SD/Accredo Specialty Pharmacy will ship SPINRAZA in a temperature-controlled container directly to your practice or facility
  - 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.

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. Perform a platelet count and coagulation laboratory testing at baseline and prior to each administration of SPINRAZA and as clinically needed.

In a clinical study, 11% of SPINRAZA-treated patients with normal or above normal platelet levels at baseline developed a platelet level below the lower limit of normal compared to zero sham-procedure control patients. No patient had a platelet count <50,000 cells per mcL and no patient developed a sustained low platelet count despite continued drug exposure.

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Confidential and proprietary to Biogen.
Submitting Claims for SPINRAZA™ (nusinersen) and Related Services
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 site of care 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 sites of care. 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.

IMPORTANT SAFETY INFORMATION (continued)
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 a clinical study, 33% of SPINRAZA-treated patients had elevated urine protein, compared to 20% of sham-control patients. In a group of later-onset SMA patients, 69% had elevated urine protein.

No elevations in serum creatinine or cystatin C were observed in studies with SPINRAZA. 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 >0.2 g/L, consider repeat testing and further evaluation.

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Confidential and proprietary to Biogen.
SUMMARY OF RELEVANT CODES FOR SPINRAZA

ICD-10-CM CODE EXAMPLES

<table>
<thead>
<tr>
<th>ICD-10-CM Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>G12.0</td>
<td>Infantile spinal muscular atrophy, type I [Werdnig-Hoffmann]</td>
</tr>
<tr>
<td>G12.1</td>
<td>Other inherited spinal muscular atrophy</td>
</tr>
<tr>
<td>G12.8</td>
<td>Other spinal muscular atrophies and related syndromes</td>
</tr>
<tr>
<td>G12.9</td>
<td>Spinal muscular atrophy, unspecified</td>
</tr>
</tbody>
</table>

Note that ICD-10-CM code G12.1 includes the following:
- Childhood form, type II spinal muscular atrophy
- Juvenile form, type III spinal muscular atrophy [Kugelberg-Welander]

HCPCS CODE EXAMPLES

<table>
<thead>
<tr>
<th>HCPCS Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>J3490</td>
<td>Unclassified drugs</td>
</tr>
<tr>
<td>J3590</td>
<td>Unclassified biologics</td>
</tr>
</tbody>
</table>

SPINRAZA is designated by a miscellaneous J-code (also referred to as unclassified J-code or Not Otherwise Classified [NOC] J-code). The miscellaneous code should be used until a permanent code is assigned by January 2018.

Though SPINRAZA is not a biologic, some payers may require that code be used for certain specialty drugs.

When submitting a claim with an NOC J-code, payers typically require supplemental product information for manual claims processing, such as the drug name, 11-digit NDC number, concentration, amount administered, and route of administration. However, specific requirements may vary by payer and should be reviewed prior to submitting a claim. In the case of a Medicare hospital outpatient claim, you may be required to use a miscellaneous C-code (C9399) rather than a J-code.


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

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CONSIDERATIONS FOR ADMINISTRATION

SPINRAZA is administered intrathecally by, or under the direction of, an HCP with experience performing lumbar punctures. In addition, providers can consider the following services for the administration of SPINRAZA, as needed:

- Sedation as indicated by the clinical condition of the patient
- Ultrasound or other imaging techniques to guide intrathecal administration of SPINRAZA, particularly in younger patients

CPT CODE MODIFIER EXAMPLES

<table>
<thead>
<tr>
<th>Modifier</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>22</td>
<td>Increased procedural services</td>
</tr>
<tr>
<td>23</td>
<td>Unusual anesthesia services</td>
</tr>
<tr>
<td>25</td>
<td>Significant, separately identifiable evaluation and management service by the same physician or other qualified HCP on the same day of procedure or other service</td>
</tr>
<tr>
<td>51</td>
<td>Multiple procedures</td>
</tr>
<tr>
<td>52</td>
<td>Reduced services</td>
</tr>
<tr>
<td>53</td>
<td>Discontinued procedure</td>
</tr>
<tr>
<td>59</td>
<td>Distinct procedural service</td>
</tr>
</tbody>
</table>

Appropriate modifier(s) can help report additional circumstances under which a specific procedure and/or ancillary services were provided.

IMPORTANT SAFETY INFORMATION (continued)

Serious adverse reactions of atelectasis were more frequent in SPINRAZA-treated patients (14%) than in control patients (5%). Because patients in the controlled study were infants, adverse reactions that are verbally reported could not be assessed in this study. In the open-label studies, the most common adverse events in later onset patients were headache (50%), back pain (41%), and post lumbar puncture syndrome (41%).

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Confidential and proprietary to Biogen.
UNIQUE BILLING CONSIDERATIONS FOR OUTPATIENT HOSPITAL-BASED FACILITIES

REVENUE CODE EXAMPLES FOR OUTPATIENT HOSPITAL-BASED FACILITIES*  

<table>
<thead>
<tr>
<th>Service Type</th>
<th>Revenue Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug Product</td>
<td>0636</td>
<td>Pharmacy (ie, drugs requiring detailed coding)</td>
</tr>
<tr>
<td>Drug Administration, Surgical</td>
<td>0331</td>
<td>Radiology/therapeutic (ie, chemotherapy injected)</td>
</tr>
<tr>
<td>Procedure, Treatment Observation</td>
<td>0361</td>
<td>Operating room services (ie, minor surgery)</td>
</tr>
<tr>
<td></td>
<td>0499</td>
<td>Ambulatory surgical care (ie, other ambulatory surgical care)</td>
</tr>
<tr>
<td></td>
<td>0760</td>
<td>Treatment/observation room (ie, general classification)</td>
</tr>
<tr>
<td></td>
<td>0762</td>
<td>Treatment/observation room (ie, observation room)</td>
</tr>
<tr>
<td>Anesthesia Services</td>
<td>0370</td>
<td>Anesthesia (ie, general classification)</td>
</tr>
<tr>
<td></td>
<td>0379</td>
<td>Anesthesia (ie, other anesthesia)</td>
</tr>
<tr>
<td>Imaging Services</td>
<td>0402</td>
<td>Other imaging services (ie, ultrasound)</td>
</tr>
<tr>
<td></td>
<td>0409</td>
<td>Other imaging services (ie, other imaging services)</td>
</tr>
</tbody>
</table>

Revenue codes are required for hospital outpatient billing and will vary depending on the revenue center to which your hospital maps SPINRAZA. Typically, SPINRAZA will be reported using the revenue codes listed above.

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

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IMPORTANT SAFETY INFORMATION (continued)

RENAL TOXICITY, including potentially fatal glomerulonephritis, has been observed after administration of some antisense oligonucleotides.

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Please see following pages for additional Important Safety Information.

Confidential and proprietary to Biogen.
CPT CODE MODIFIER FOR THE TECHNICAL COMPONENT

<table>
<thead>
<tr>
<th>Modifier¹⁶</th>
<th>Description¹⁶</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC</td>
<td>Technical component</td>
</tr>
</tbody>
</table>

For procedure codes with professional and technical components, outpatient facilities may use the TC modifier to bill for a technical component of a procedure associated with SPINRAZA administration in order to receive reimbursement for the facility, equipment, film processing, and/or technician services.

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.

<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>J3490</td>
<td>Field 44</td>
<td>2400</td>
<td>SV202-2</td>
</tr>
<tr>
<td>HCPCS Level II Code Units</td>
<td>1</td>
<td>Field 46</td>
<td>2400</td>
<td>SV205</td>
</tr>
<tr>
<td>Additional Product Information</td>
<td>SPINRAZA 64406-0058-01 12 mg/5 mL, 5 mL intrathecal inj</td>
<td>Field 80</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 44</td>
<td>2400</td>
<td>SV202-2</td>
</tr>
<tr>
<td>ICD-10-CM Code (primary)</td>
<td>G12.0</td>
<td>Field 67</td>
<td>2300</td>
<td>HI01-2</td>
</tr>
<tr>
<td>Bill Type Code</td>
<td>Provider specificᵇ</td>
<td>Field 4</td>
<td>2300</td>
<td>CLM05-1</td>
</tr>
<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>

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

The table above 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.

IMPORTANT SAFETY INFORMATION (continued)

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.

Please see following pages for additional Important Safety Information.
SAMPLE CMS-1450/UB-04 CLAIM FORM
FOR OUTPATIENT HOSPITAL-BASED FACILITIES

Field 46: Enter the appropriate number of units of service. 
NOTE: 1 billing unit is typically reported with a miscellaneous/unclassified J-code.

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)

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

Field 80: Enter additional product information as required by the patient’s payer for claims with a miscellaneous/unclassified J-code, such as the drug name, 11-digit NDC number, concentration, amount, and route of administration; for example:
- SPINRAZA 64406-0058-01 12 mg/5 mL, 5 mL intrathecal inj

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)
- 0762, Treatment/observation room (ie, observation room)

For Field 43, NDC reporting requirements may vary by payer. For more examples, please see page 41.

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).

Field 44: Enter appropriate CPT/HCPCS codes and modifiers; for example:
- J3490, Unclassified drugs
- 96450, Chemotherapy administration, into CNS (eg, intrathecal), requiring spinal puncture

NOTE: Other CPT codes may apply; for example:
- 00635, Anesthesia for procedures in lumbar region; diagnostic or therapeutic lumbar puncture
- 76942, Ultrasonic guidance for needle placement (eg, biopsy, aspiration, injection, localization device), imaging supervision, and interpretation
- 99218, Initial observational care, per day, for the evaluation and management of a patient, which requires these 3 key components: a detailed or comprehensive history, a detailed or comprehensive examination, and medical decision-making that is straightforward or of low complexity

For more examples, please see page 39.

Field 8: Enter additional product information as required by the patient’s payer for claims with a miscellaneous/unclassified J-code, such as the drug name, 11-digit NDC number, concentration, amount, and route of administration; for example:
- SPINRAZA 64406-0058-01 12 mg/5 mL, 5 mL intrathecal inj

NOTE: Requirements may vary by payer.

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

Please see following pages for additional Important Safety Information.
UNIQUE BILLING CONSIDERATIONS FOR PROFESSIONAL SERVICES

CPT CODE MODIFIER FOR THE PROFESSIONAL COMPONENT

<table>
<thead>
<tr>
<th>Modifier¹⁶</th>
<th>Description¹⁶</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.

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>Examples of Relevant Codes for SPINRAZA and Electronic Billing Locations for Professional Services¹⁶,¹⁸,¹⁹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Information</td>
</tr>
<tr>
<td>-------------</td>
</tr>
<tr>
<td>CPT Code(s)</td>
</tr>
<tr>
<td>ICD-10-CM Code (primary)</td>
</tr>
<tr>
<td>Place of Service Code</td>
</tr>
</tbody>
</table>

ᵃA 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).²⁰

IMPORTANT SAFETY INFORMATION (continued)

The most common adverse reactions that occurred in the controlled study in at least 20% of SPINRAZA-treated patients and occurred at least 5% more frequently than in control patients were upper respiratory infection (39% vs 34%), lower respiratory infection (43% vs 29%), and constipation (30% vs 22%). Serious adverse reactions of atelectasis were more frequent in SPINRAZA-treated patients (14%) than in control patients (5%). Because patients in the controlled study were infants, adverse reactions that are verbally reported could not be assessed in this study. In the open-label studies, the most common adverse events in later onset patients were headache (50%), back pain (41%) and post lumbar puncture syndrome (41%).

Please see following pages for additional Important Safety Information.

Confidential and proprietary to Biogen.
### Sample CMS-1500 Claim Form

**For Professional Services**

![CMS-1500 Claim Form]

#### Field 21A:
Enter the appropriate primary ICD-10-CM diagnosis code; for example:
- **G12.0**, Infantile spinal muscular atrophy, type I [Werdnig-Hoffmann]

For more examples, please see page 38.

#### Field 24B:
Enter the appropriate place of service code; for example:
- **19**, Off-campus outpatient hospital
- **22**, On-campus outpatient hospital
- **21**, Inpatient hospital

#### Field 24D:
Enter appropriate CPT/HCPCS codes and modifiers; for example:
- **96450**, Chemotherapy administration, into CNS (eg, intrathecal), requiring spinal puncture
- **76942**, Ultrasonic guidance for needle placement (eg, biopsy, aspiration, injection, localization device), imaging supervision, and interpretation
- **26**, Professional component
- **00635**, Anesthesia for procedures in lumbar region; diagnostic or therapeutic lumbar puncture

**NOTE:** Other CPT codes and modifiers may apply.

For more examples, please see pages 38-40.

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Please see following pages for additional Important Safety Information.

Confidential and proprietary to Biogen.
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>
</tr>
</thead>
<tbody>
<tr>
<td>HCPCS Level II Code</td>
<td>J3490</td>
<td>Field 24D</td>
<td>2400</td>
<td>SV101</td>
</tr>
<tr>
<td>HCPCS Level II Code Units</td>
<td></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>
<td>Provider-specific&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Field 24B</td>
<td>2300</td>
<td>CLM05-1</td>
</tr>
</tbody>
</table>

<sup>a</sup>A 2-digit place of service code documents site of care. Relevant examples for professional services include 11 (office) and 24 (ASC). 20

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. Perform a platelet count and coagulation laboratory testing at baseline and prior to each administration of SPINRAZA and as clinically needed.

In a clinical study, 11% of SPINRAZA-treated patients with normal or above normal platelet levels at baseline developed a platelet level below the lower limit of normal compared to zero sham-procedure control patients. No patient had a platelet count <50,000 cells per mcL and no patient developed a sustained low platelet count despite continued drug exposure.

Please see following pages for additional Important Safety Information.

Confidential and proprietary to Biogen.
SAMPLE CMS-1500 CLAIM FORM
FOR PHYSICIAN OFFICES AND FREESTANDING ASCs

**Field 21A**: Enter the appropriate primary ICD-10-CM diagnosis code; for example:
- G12.0, Infantile spinal muscular atrophy, type I [Werdnig-Hoffmann]
For more examples, please see page 38.

**Field 19**: Enter additional product information as required by the patient's payer for claims with a miscellaneous/unclassified J-code, such as the drug name, 11-digit NDC number, concentration, amount, and route of administration; for example:
- SPINRAZA 64406-0058-01 12 mg/5 mL, 5 mL intrathecal inj

**Note**: Requirements may vary by payer.

**Red shaded areas for fields 24A-D**: NDC reporting requirements may vary by payer

**Field 24B**: Enter the appropriate place of service code; for example:
- 11, Office
- 24, ASC

**Field 24G**: Enter the appropriate number of units of service.
Note: 1 billing unit is typically reported with a miscellaneous/unclassified J-code.

**Field 24D**: Enter appropriate CPT/HCPCS codes and modifiers; for example:
- J3490, Unclassified drugs
- 96450, Chemotherapy administration, into CNS (eg, intrathecal), requiring spinal puncture

**Note**: Other CPT codes and modifiers may apply, for example:
- 00635, Anesthesia for procedures in lumbar region; diagnostic or therapeutic lumbar puncture
- 76942, Ultrasound guidance for needle placement (eg, biopsy, aspiration, injection, localization device), imaging supervision, and interpretation

For more examples, please see page 38-40.
**UNIQUE BILLING CONSIDERATIONS FOR INPATIENT HOSPITAL FACILITIES**

**REVENUE CODE EXAMPLES FOR INPATIENT HOSPITAL FACILITIES**

<table>
<thead>
<tr>
<th>Service Type</th>
<th>Revenue Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug Product</td>
<td>0636</td>
<td>Pharmacy (ie, drugs requiring detailed coding)</td>
</tr>
<tr>
<td>Room and Board</td>
<td>0101</td>
<td>All-inclusive rate (ie, all-inclusive room and board)</td>
</tr>
<tr>
<td>Drug Administration, Surgical Procedure, Treatment Observation</td>
<td>0272, 0331, 0360, 0369</td>
<td>Medical/surgical supplies (ie, sterile supply), Radiology/therapeutic, Operating room services (ie, general classification), Operating room services (ie, other operating room services)</td>
</tr>
<tr>
<td>Anesthesia Services</td>
<td>0370</td>
<td>Anesthesia (ie, general classification)</td>
</tr>
<tr>
<td>Imaging Services</td>
<td>0402, 0409</td>
<td>Other imaging services (ie, ultrasound), Other imaging services (ie, other imaging services)</td>
</tr>
</tbody>
</table>

Revenue codes are required for hospital inpatient billing and will vary depending on the revenue center to which your hospital maps SPINRAZA. Typically, SPINRAZA will be reported using the revenue codes listed above.

**ICD-10-PCS PROCEDURE CODE EXAMPLES**

<table>
<thead>
<tr>
<th>Procedure Type</th>
<th>ICD-10-PCS Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intrathecal Drug Administration</td>
<td>3E0R3GC</td>
<td>Introduction of other therapeutic substance into spinal canal, percutaneous approach</td>
</tr>
<tr>
<td>Imaging Procedure/Guidance</td>
<td>BR13YZZ, BR49ZZZ</td>
<td>Fluoroscopy of lumbar disc(s) using other contrast, Ultrasonography of lumbar spine</td>
</tr>
<tr>
<td>Inhalation Anesthesia</td>
<td>3E0F7DZ</td>
<td>Introduction of inhalation anesthetic into respiratory tract, via natural or artificial opening</td>
</tr>
</tbody>
</table>

When SPINRAZA is administered in the inpatient setting, appropriate inpatient procedure codes will need to be reported on the claim. Typically, SPINRAZA administration procedures will be reported using the ICD-10-PCS codes listed above.

ICD-10-PCS=International Classification of Diseases, Tenth Revision, Procedure Coding System.

**IMPORTANT SAFETY INFORMATION (continued)**

**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 a clinical study, 33% of SPINRAZA-treated patients had elevated urine protein, compared to 20% of sham-control patients. In a group of later-onset SMA patients, 69% had elevated urine protein.

No elevations in serum creatinine or cystatin C were observed in studies with SPINRAZA. 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 >0.2 g/L, consider repeat testing and further evaluation.

Please see following pages for additional Important Safety Information.

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CODING SUMMARY FOR ELECTRONIC CLAIM SUBMISSION BY INPATIENT HOSPITAL FACILITIES

The table below provides examples of relevant codes, along with corresponding locations, for paper and electronic claims submitted by inpatient hospital facilities for SPINRAZA and related administration services (as part of a planned inpatient stay).

Requirements and location of information will vary by payer.

<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>J3490</td>
<td>Field 44</td>
<td>2400</td>
<td>SV202-2</td>
</tr>
<tr>
<td>HCPCS Level II Code Units</td>
<td></td>
<td>Field 46</td>
<td>2400</td>
<td>SV205</td>
</tr>
<tr>
<td>Additional Product Information</td>
<td>SPINRAZA 64406-0058-01</td>
<td>Field 80</td>
<td>2300</td>
<td>NTE</td>
</tr>
<tr>
<td></td>
<td>12 mg/5 mL, 5 mL intrathecal inj</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICD-10-PCS Code(s)</td>
<td>3E0R3GC BR13YZZ 3E0F7DZ</td>
<td>Fields 74-74E</td>
<td>2300</td>
<td>HI01-2 through HI05-4</td>
</tr>
<tr>
<td></td>
<td>Other ICD-10-PCS codes may apply, as appropriate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICD-10-CM Code (primary)</td>
<td>G12.0</td>
<td>Field 67</td>
<td>2300</td>
<td>HI01-2</td>
</tr>
<tr>
<td>Bill Type Code</td>
<td>Provider-specific&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Field 4</td>
<td>2300</td>
<td>CLM05-1</td>
</tr>
<tr>
<td>Revenue Code(s)</td>
<td>0101, 0272, 0360, 0370, 0409, 0636</td>
<td>Field 42</td>
<td>2400</td>
<td>SV201</td>
</tr>
<tr>
<td></td>
<td>Other revenue codes may apply, as appropriate</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>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 inpatient hospital facilities include 011X (hospital inpatient) and 014X (hospital other), where X represents the sequence of the bill in this particular episode of care (e.g., "1" for admit through discharge claim).<sup>7</sup>

IMPORTANT SAFETY INFORMATION (continued)

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.

Please see following pages for additional Important Safety Information.

Confidential and proprietary to Biogen.
SAMPLE CMS-1450/UB-04 CLAIM FORM
FOR INPATIENT HOSPITAL FACILITIES

Field 4: Enter the appropriate type of bill code; for example:
- 011X, Hospital inpatient
- 014X, Hospital other

Field 44: Enter the appropriate HCPCS code corresponding to the revenue code 0636 (Pharmacy: drugs requiring detailed coding) in order to provide detailed level coding; for example:
- J3490, Unclassified drugs

Fields 74-74E: Enter appropriate principal and other ICD-10-PCS procedure codes (along with corresponding dates); for example:
- 3E0R3GC, Introduction of other therapeutic substance into spinal canal, percutaneous approach
- BR13YZZ, Fluoroscopy of lumbar disc(s) using other contrast
- 3E0F7DZ, Introduction of inhalation anesthetic into respiratory tract, via natural or artificial opening

NOTE: Other ICD-10-PCS procedure codes may apply; for example:
- BR49ZZZ, Ultrasonography of lumbar spine

Field 80: Enter additional product information as required by the patient’s payer for claims with a miscellaneous/unclassified J-code, such as the drug name, 11-digit NDC number, concentration, amount, and route of administration; for example:
- SPINRAZA 64406-0058-01 12 mg/5 mL, 5 mL intrathecal inj

NOTE: Requirements may vary by payer.

Please see following pages for additional Important Safety Information.
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CLAIM SUBMISSION, TRACKING, AND APPEALS 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 benefit investigation process, confirm that you have identified the following:
    - Coverage and any prior authorization restrictions, medical necessity or exception requirements
    - 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, prior authorization number, 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

IMPORTANT SAFETY INFORMATION (continued)

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.

Please see following pages for additional Important Safety Information.

Confidential and proprietary to Biogen.
CLAIM TRACKING CONSIDERATIONS

Tracking payer reimbursement for therapies and treatments is key for facilitating appropriate payment. It is important for offices to check payers’ EOB/remittance advice statements for accuracy in order to detect any claims processing errors or inappropriate adjustments and to monitor for denials.

The following is a list of considerations for tracking claims:

- Establish a routine procedure for monitoring the status of claims
- Maintain a log of all correspondence with each payer for each claim. This will enable your office to monitor payer contract compliance
- Review payer EOB against contracted fee schedules
- Evaluate payer responsiveness in addressing reimbursement issues
- Establish a procedure for addressing claims denials and submitting appeals

IMPORTANT SAFETY INFORMATION (continued)

The most common adverse reactions that occurred in the controlled study in at least 20% of SPINRAZA-treated patients and occurred at least 5% more frequently than in control patients were upper respiratory infection (39% vs 34%), lower respiratory infection (43% vs 29%), and constipation (30% vs 22%). Serious adverse reactions of atelectasis were more frequent in SPINRAZA-treated patients (14%) than in control patients (5%). Because patients in the controlled study were infants, adverse reactions that are verbally reported could not be assessed in this study. In the open-label studies, the most common adverse events in later onset patients were headache (50%), back pain (41%) and post lumbar puncture syndrome (41%).

Please see following pages for additional Important Safety Information.

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APPEALS CONSIDERATIONS CHECKLIST

If a claim has been denied, you can request an appeal. There are several common reasons that claims are denied, such as 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.

- Review the EOB to understand the reason for the denial

  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 (e.g., 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 second claim is denied, consider an external review and inform your Biogen representatives

External claim review

Most states have their own set of rules for requests for external claim reviews, which are conducted by an independent party. Requests for external reviews typically must be submitted within 60 days of receiving a payer's decision of a claim denial and will take no more than 60 days to complete after the request was received. The external reviewer's decision is considered final.23

For more information about an external claim review, go to https://www.healthcare.gov/appeal-insurance-company-decision/external-review/ or talk to your Biogen Rare Disease Reimbursement Manager for assistance.

The link above will take you to a website that is outside the control of Biogen. Links are provided as a courtesy for informational purposes only. We do not make or imply any endorsement of external websites.

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. Perform a platelet count and coagulation laboratory testing at baseline and prior to each administration of SPINRAZA and as clinically needed.

Please see following pages for additional Important Safety Information.

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Appendix
Important Safety Information (continued)

In a clinical study, 11% of SPINRAZA-treated patients with normal or above normal platelet levels at baseline developed a platelet level below the lower limit of normal compared to zero sham-procedure control patients. No patient had a platelet count <50,000 cells per mcL and no patient developed a sustained low platelet count despite continued drug exposure.

Please see following pages for additional Important Safety Information.

Confidential and proprietary to Biogen.
Sample Letter of Medical Necessity

The Use of SPINRAZA™ (nusinersen) for Spinal Muscular Atrophy

Date:
[Insert Name of Medical Director]  RE: Patient Name [ ]
[Insurance Company]  Policy Number [ ]
[Address]  Claim Number [ ]
[City, State, Zip]

Dear [Insurance Company]:

I am writing this letter of medical necessity to provide information related to the treatment of [insert patient name] with SPINRAZA™ (nusinersen), the only US Food and Drug Administration (FDA)-approved treatment for spinal muscular atrophy (SMA).

I would like to provide the following information about the potential benefits of SPINRAZA in patients with SMA:

1. SMA Pathophysiology

SMA is a genetic neuromuscular disease characterized by degeneration of motor neurons in the anterior horn of the spinal cord. SMA is characterized by progressive symmetrical weakness and atrophy of the proximal voluntary muscles of legs, arms, and eventually of the entire trunk during disease progression. Infants and...

Please contact your Biogen representative for a copy of this document.

Important Safety Information (continued)

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 a clinical study, 33% of SPINRAZA-treated patients had elevated urine protein, compared to 20% of sham-control patients. In a group of later-onset SMA patients, 69% had elevated urine protein.

No elevations in serum creatinine or cystatin C were observed in studies with SPINRAZA. 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 >0.2 g/L, consider repeat testing and further evaluation.

Please see following pages for additional Important Safety Information.

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REFERENCES


IMPORTANT SAFETY INFORMATION (continued)

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.

Please see following page for additional Important Safety Information.

Confidential and proprietary to Biogen.
INDICATION
SPINRAZA 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. Perform a platelet count and coagulation laboratory testing at baseline and prior to each administration of SPINRAZA and as clinically needed.

In a clinical study, 11% of SPINRAZA-treated patients with normal or above normal platelet levels at baseline developed a platelet level below the lower limit of normal compared to zero sham-procedure control patients. No patient had a platelet count <50,000 cells per mcL and no patient developed a sustained low platelet count despite continued drug exposure.

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 a clinical study, 33% of SPINRAZA-treated patients had elevated urine protein, compared to 20% of sham-control patients. In a group of later-onset SMA patients, 69% had elevated urine protein.

No elevations in serum creatinine or cystatin C were observed in studies with SPINRAZA. 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 >0.2 g/L, consider repeat testing and further evaluation.

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.

The most common adverse reactions that occurred in the controlled study in at least 20% of SPINRAZA-treated patients and occurred at least 5% more frequently than in control patients were upper respiratory infection (39% vs 34%), lower respiratory infection (43% vs 29%), and constipation (30% vs 22%). Serious adverse reactions of atelectasis were more frequent in SPINRAZA-treated patients (14%) than in control patients (5%). Because patients in the controlled study were infants, adverse reactions that are verbally reported could not be assessed in this study. In the open-label studies, the most common adverse events in later onset patients were headache (50%), back pain (41%) and post lumbar puncture syndrome (41%).

Please see full Prescribing Information for additional Important Safety Information.

Confidential and proprietary to Biogen.
Please see full Prescribing Information for additional Important Safety Information.
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**
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

**DOSE 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 (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, upper respiratory infection, and constipation (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Biogen at 1-800-456-2255 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 12/2016
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.
- 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.

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 a clinical study, 6 of 56 (11%) SPINRAZA-treated patients with normal or above normal platelet levels at baseline developed a platelet level below the lower limit of normal, compared to 0 of 28 sham-procedure control patients. No patient had a platelet count less than 50,000 cells per microliter in this study and no patient developed a sustained low platelet count despite continued drug exposure.

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 a clinical study (mean treatment exposure 7 months), 17 of 51 (33%) SPINRAZA-treated patients had elevated urine protein, compared to 5 of 25 (20%) sham-control patients. In a group of later-onset SMA patients (mean treatment exposure 34 months), 36 of 52 (69%) had elevated urine protein. No elevations in serum creatinine or cystatin C were observed in these studies. 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 173 patients (50% male, 82% Caucasian), including 120 exposed for at least 6 months and 83 exposed for at least 1 year. The safety of SPINRAZA was studied in infants with symptomatic SMA, approximately 1 month to 8 months of age at study entry; in a sham-controlled trial (n=80 for SPINRAZA, n=41 for control); in open-label studies in presymptomatic and symptomatic infants (n=37), and in open-label studies in later onset patients (n=56, 2 to 15 years of age at study entry). In the controlled study in symptomatic infants, 41 patients were exposed for at least 6 months and 19 patients were exposed for at least 12 months.

In the controlled study, 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%).

In the controlled study, 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, upper respiratory infection, and constipation. Serious adverse reactions of atelectasis were more frequent in SPINRAZA-treated patients (14%) than in control patients (5%). Because patients in the controlled study 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 in the Controlled Study in Infants with Symptomatic SMA

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>SPINRAZA 12 mg&lt;sup&gt;1&lt;/sup&gt;</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&lt;sup&gt;2&lt;/sup&gt;</td>
<td>43</td>
<td>29</td>
</tr>
<tr>
<td>Upper respiratory infection&lt;sup&gt;3&lt;/sup&gt;</td>
<td>39</td>
<td>34</td>
</tr>
<tr>
<td>Constipation</td>
<td>30</td>
<td>22</td>
</tr>
<tr>
<td>Teething</td>
<td>14</td>
<td>7</td>
</tr>
<tr>
<td>Upper respiratory tract congestion</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Aspiration</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Ear infection</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Scoliosis</td>
<td>5</td>
<td>2</td>
</tr>
</tbody>
</table>

<sup>1</sup> Four loading doses followed by 12 mg (5 mL) once every 4 months

<sup>2</sup> Includes pneumonia, bronchiolitis, pneumonia viral, respiratory syncytial virus bronchiolitis, lower respiratory tract infection, pneumonia bacterial, bronchitis, bronchitis viral, pneumonia moraxella, pneumonia parainfluenzae viral, lower respiratory tract infection viral, lung infection, pneumonia influenza, pneumonia pseudomonal, pneumonia respiratory syncytial viral

<sup>3</sup> Includes upper respiratory tract infection, nasopharyngitis, rhinitis, pharyngitis, or tracheitis

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.

The most common adverse events in the open-label studies in later onset patients were headache (50%), back pain (41%) and post lumbar puncture syndrome (41%). Most of these events
occurred within 5 days of lumbar puncture. Other adverse events in these patients were consistent with adverse reactions observed in the controlled study.

6.2 Immunogenicity

The immunogenic response to nusinersen was determined in 126 patients with baseline and post-baseline plasma samples evaluated for anti-drug antibodies (ADAs). Five (4%) patients developed treatment-emergent ADAs, of which 3 were transient and 2 were considered to be persistent. There are insufficient data to evaluate an effect of ADAs on clinical response, adverse events, or the pharmacokinetic profile of nusinersen.

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. In addition, 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 SPINRAZA in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

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. No adverse effects on embryofetal development were observed in animal studies in which nusinersen was administered by subcutaneous injection to mice and rabbits during pregnancy (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.

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. 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

SMA is largely a disease of children and young adults; therefore, there is no geriatric experience with SPINRAZA.

11 DESCRIPTION

SPINRAZA contains nusinersen, which 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
In 121 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 5% of 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 $T_{\text{max}}$ values ranged from 1.7 to 6.0 hours. Mean plasma $C_{\text{max}}$ 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 a double-blind, sham-procedure controlled clinical trial in symptomatic infantile-onset SMA patients and was supported by open-label clinical trials conducted in presymptomatic and symptomatic SMA patients.

14.1 Clinical Trial in Infantile-Onset SMA

This study 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 SPINRAZA or sham injection.

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, 44% were male and 56% were female. Age at first treatment ranged from 30 to 262 days (median 181). Eighty-seven (87%) of subjects were Caucasian, 2% were Black, and 4% were Asian. 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 (2 copies in 98% of subjects in both groups). 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 a motor milestone response in the SPINRAZA group compared to the sham-control group (see Table 2). 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.

Although not statistically controlled for multiple comparisons at the interim 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 2.

### Table 2. Motor Milestone Response and CHOP-INTEND Results

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>SPINRAZA-treated patients (n=52)</th>
<th>Sham-control patients (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Motor Milestone (HINE Section 2)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Achievement of a motor milestone response</td>
<td>21 (40%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>p&lt;0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CHOP-INTEND Improvement from Baseline</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At least 4-points</td>
<td>33 (63%)</td>
<td>1 (3%)</td>
</tr>
<tr>
<td><strong>CHOP-INTEND Worsening from Baseline</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At least 4-points</td>
<td>2 (4%)</td>
<td>12 (40%)</td>
</tr>
</tbody>
</table>

1Analyses included all subjects who were alive with the opportunity for at least a 6-month (Day 183) assessment and all subjects who died or withdrew from the study at the time of the interim analysis

2Not statistically controlled for multiple comparisons at interim analysis

**Figure 1. Net Change from Baseline in Total Motor Milestone Score (HINE) by Percent of Subjects in the Interim Efficacy Set**

*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.

The results of the controlled trial in infantile-onset SMA patients were supported by open-label uncontrolled trials conducted in symptomatic SMA patients who ranged in age from 30 days to 15 years at the time of first dose, and in presymptomatic patients, who ranged in age from 8 days to 42 days at the time of first dose. The patients in these studies had or were likely to develop...
Type 1, 2, or 3 SMA. Some patients achieved milestones such as ability to sit unassisted, stand, or walk when they would otherwise be unexpected to do so, maintained milestones at ages when they would be expected to be lost, and survived to ages unexpected considering the number of SMN2 gene copies of patients enrolled in the studies.

The overall findings of the controlled trial in infantile-onset SMA and the open-label uncontrolled trials support the effectiveness of SPINRAZA across the range of SMA patients, and appear to support the early initiation of treatment with SPINRAZA.

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)].
Manufactured for:
Biogen Inc.
Cambridge, MA 02142
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