OPTUMRx

Therapeutic Class Overview
Agent for Spinal Muscular Atrophy: SPINRAZA (nusinersen)

INTRODUCTION

- Spinal muscular atrophy (SMA) is a serious neuromuscular disease characterized by the degeneration of motor neurons in the spinal cord and brainstem, leading to progressive muscular atrophy and weakness (*Genetics Home Reference 2017, Wang et al 2007*). SMA is caused by an inherited genetic mutation, and is the most common genetic cause of infant death (*Markowitz et al 2012*).
- SMA is an autosomal recessive inherited disorder. The overall incidence is between 4 and 10 per 100,000 live births, and 1 person in 50 to 90 is a carrier of a mutation that can cause SMA (*Bodamer 2017, Wang et al 2007*).
- There are several forms of SMA with varying degrees of severity and ages of onset. Please see Table 1 for an overview of the SMA clinical classifications.
- Type 1 SMA is the most common form, affecting approximately 58% of patients. Type 2 and Type 3 occur in approximately 29% and 13% of patients, respectively, and type 4 is less common (< 5%) (*Food and Drug Administration [FDA] medical review 2016*). Mothers may notice a decrease of fetal movement in late pregnancy, and some experts classify prenatal onset as type 0 SMA, which is very rare (*Bodamer 2017, FDA medical review 2016*).

Table 1. Clinical Classification of SMA (*Bodamer 2017, FDA medical review 2016, Markowitz et al 2012, Wang et al 2007*)

SMA Type	Age at Onset	Typical Life Span	Clinical Features
Type 0 (Prenatal)	Prenatal	< 6 months	Mostly unable to achieve motor milestones. Severe weakness at birth and profound hypotonia. Early respiratory failure.
Type 1 (Severe)	0 to 6 months	< 2 years (without respiratory support)	Never sits unsupported. Weakness and hyporeflexia. Weakness of mouth and throat muscles leads to a weak cry, poor suck and swallow reflexes, pooling of secretions, and aspiration. Respiratory failure.
Type 2 (Intermediate)	6 to 18 months	~ 70% alive at age 25 years	Sits independently, but never stands or walks. Proximal weakness, hypotonia and hyporeflexia. Weakness and swallowing difficulties may lead to poor weight gain. Difficulty coughing and clearing secretions. Scoliosis may be present.
Type 3 (Mild)	> 18 months	Almost normal	Stands and walks. Some patients lose the ability to walk in childhood; others in adolescence or adulthood. Swallowing and respiratory difficulties are less common, but may occur. Scoliosis, muscle aching, and joint overuse symptoms are common.
Type 4 (Adult)	> 21 years	Normal	Adult onset of progressive weakness that can lead to eventual loss of ambulation after years. Mild motor impairment; no respiratory or gastrointestinal problems.

- SMA is usually caused by a deletion or mutation in the survival motor neuron 1 (*SMN1*) gene on chromosome 5q. The mutation is most commonly a homozygous deletion involving exon 7 of the gene (*Bodamer 2017*).
- The *SMN1* gene is responsible for the production of SMN protein, and mutations in the *SMN1* gene lead to a shortage of the protein. Without this protein, motor neurons degenerate and nerve impulses are not carried between the brain and muscles. The result is muscle weakness and impaired movement (*Bodamer 2017, Genetics Home Reference 2017*).

- There is also a modifying (or "backup") gene called *SMN2*, which has > 99% similarity to *SMN1*. Although *SMN1* is normally the active gene for SMN protein production, there is a small amount of protein generated by *SMN2* that may modulate the clinical severity of SMA (*FDA summary review 2016, Bodamer 2017*). This backup gene is the target for the mechanism of action of nusinersen.
    - *SMN2* produces several different versions of the SMN protein; however, only one form is full-length and functional (*Genetics Home Reference 2017*). The majority of *SMN2* messenger RNA (mRNA) transcripts do not contain exon 7 and do not generate full-length functional SMN protein (*Finkel et al 2016*).
    - The number of *SMN2* gene copies varies among individuals, and patients with a higher number of *SMN2* gene copies tend to have less severe SMA. Most patients with types 0, 1, 2, 3, and 4 SMA have 1, 2, 3, 4, and ≥ 4 copies of *SMN2*, respectively (*FDA summary review 2016*). However, there is variability to this, and predicting the clinical phenotype using *SMN2* copy number is not recommended (*Wang et al 2007*).
- Nusinersen is an antisense oligonucleotide designed to treat SMA caused by mutations in chromosome 5q that lead to SMN protein deficiency. Nusinersen binds to sites within *SMN2* pre-mRNA, promoting inclusion of exon 7 in *SMN2* mRNA transcripts and increasing production of full-length, functional SMN protein (*Finkel et al 2016*).
- Prior to the FDA approval of nusinersen, there were no specific treatments for SMA (*FDA news release 2016*). Treatment has been supportive, focusing on providing nutrition and respiratory assistance and preventing or treating the complications of weakness. Nonpharmacologic treatments include physical therapy, spinal bracing, chest physiotherapy, and respiratory support (*Bodamer 2017*).
- Nusinersen was approved by the FDA in December 2016 as a treatment for SMA. The FDA granted nusinersen fast track designation, orphan drug designation, and priority review (*FDA news release 2016*).
- Nusinersen is available through a limited distribution process. The provider can order the product through CuraScript SD (a specialty distributor) or from Accredo Specialty Pharmacy. Nusinersen will be shipped directly to the practice or facility (*Spinraza reimbursement guide 2016*).
- Medispan Class: Spinal Muscular Atrophy Agents

Table 2. Medications Included Within Class Review

Drug	Manufacturer	FDA Approval Date	Generic Availability
SPINRAZA™ (nusinersen)	Biogen	12/23/2016	-

(Drugs@FDA, 2017)

INDICATIONS

Table 3. FDA Approved Indications

Indication	SPINRAZA (nusinersen)
Treatment of SMA in pediatric and adult patients	✔

(SPINRAZA prescribing information, 2016)

- Information on indications, pharmacology, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

Clinical Trials

- Please see the appendix for a description of key motor function endpoints.
- The pivotal trial leading to FDA approval of nusinersen was the ENDEAR trial, a Phase 3, double-blind, sham-controlled trial (*Finkel et al 2017, Spinraza dossier 2016*). This trial enrolled patients who were 7 months or younger at screening, with onset of clinical signs and symptoms consistent with SMA at ≤ 6 months of age. Patients were treated with 12 mg scaled equivalent intrathecal doses of nusinersen (adjusted based on the patient's age), with loading doses on days 1, 15, 29, and 64, followed by maintenance dosing every 4 months (days 183 and 302). Control patients received a sham procedure (skin prick).
    - At the planned interim analysis after approximately 14 months of follow-up, 78 patients (51 and 27 in the nusinersen and control arms, respectively) had reached a 6-month evaluation and were included in the interim efficacy set. Of these patients, 1 patient in each group had voluntarily withdrawn from the study, and

21 patients had died (11 of 51 [21.6%] in the nusinersen group and 10/27 [37.0%] in the control group); thus, 55 patients were included in the interim efficacy set for motor milestone change assessments.
    - The primary endpoints were 1) the proportion of motor milestone responders, based on the Hammersmith Infant Neurological Examination (HINE) section 2 (HINE-2), and 2) event-free survival: time to death or permanent ventilation (≥ 16 hours ventilation/day for > 21 days or tracheostomy).
        - The proportion of patients achieving a motor milestone response was 41% in the nusinersen group and 0% in the control group (p = 0.000027). Positive changes in motor milestones were observed for most patients who received nusinersen, whereas most patients who received the control had no change or a decline from baseline.
        - Patients treated with nusinersen had significantly greater event-free survival (61%) than control patients (32%) (hazard ratio [HR], 0.53; p = 0.0046).
    - Secondary endpoints supported the primary results.
    - Based on positive results at the interim analysis, the study was suspended prior to its planned end.
- The CHERISH trial, which was another Phase 3, double-blind, sham-controlled trial, evaluated the use of nusinersen in later-onset SMA (*Biogen Medical Information 2016, Spinraza dossier 2016*). It enrolled patients aged 2 to 12 years with an onset of SMA at > 6 months of age. Patients received nusinersen 12 mg intrathecally (n = 84 at interim analysis) or sham-control (n = 42 at interim analysis) on days 1, 29, 85, and 274.
    - Key endpoints to be assessed (each after 15 months of treatment) included the change in the Hammersmith Functional Motor Scale – Expanded (HFMSE) score (a measurement of ability to perform activities) (primary endpoint), achievement of motor milestones, and the upper limb module (ULM) (an assessment of upper limb functional abilities).
    - The length of follow-up was approximately 16 months.
    - In a pre-planned interim analysis, there was a difference of 5.9 points in the HFMSE at 15 months between the nusinersen and control groups (p = 0.0000002). Patients in the nusinersen group experienced a mean improvement of 4.0 points, and patients in the control group experienced a mean decline of 1.9 points.
    - Results for other endpoints were consistent with a favorable response to nusinersen compared to control (specific results not yet reported).
- Additional open-label, single-arm, phase 1 and 2 studies offer further support for the use of nusinersen in SMA patients.
    - A phase 2 study (CS3A), evaluating 20 patients at the interim analysis, enrolled patients aged 3 weeks to ≤ 7 months with SMA symptom onset between 3 weeks and 6 months (*Finkel et al 2016, Spinraza dossier 2016*). The interim analysis was conducted approximately 18 months after the last patient was enrolled. In 16 of 19 patients treated with nusinersen, incremental improvement in HINE-2 motor milestones was demonstrated compared to baseline. Secondary endpoints, including an additional motor function scale and an analysis of death or permanent ventilation, supported the effectiveness of nusinersen when compared to a natural history case series.
    - A phase 2 study (NURTURE), evaluating 17 patients at the interim analysis, enrolled pre-symptomatic patients aged ≤ 6 weeks with genetic documentation of SMA (*Bertini et al 2016, Spinraza dossier 2016*). Patients were identified based on an affected sibling, newborn screening, or prenatal screening. At the time of the interim analysis, 13, 10, and 5 patients had reached days 64, 183, and 302 of the study, respectively. No patients receiving nusinersen met the endpoint of death or respiratory intervention. Improvement in HINE motor milestones were achieved by 12 of 13 patients at day 64, 10 of 10 patients at day 183, and 5 of 5 patients at day 302, indicating achievement of age-appropriate motor development. Secondary motor function endpoints supported the primary endpoint.
    - An additional report evaluated 28 patients aged 2 to 15 years who had been enrolled in a Phase 1/2a study (CS2) and followed into a phase 1 extension study (CS12) (*Darras et al 2016, Spinraza dossier 2016*). The primary objective of these studies was to assess the safety and tolerability of nusinersen in patients with type 2 or 3 SMA; efficacy endpoints were considered exploratory. The length of follow-up was approximately 8 months in study CS2 and 24 months in study CS12. In patients with type 2 SMA, improvements were observed in motor function over time based on results of the HFMSE and the ULM. In patients with type 3 SMA, HFMSE scores were stable and increases were observed in the 6-minute walk test (6MWT).
- Although nusinersen has not been studied in adults or patients with type 4 SMA, its indication is for the treatment of SMA in pediatric and adult patients. The FDA medical review noted that the underlying cause of SMA (a shortage of

SMN protein) is common to patients with all SMA types, and it is reasonable to expect that nusinersen should provide clinical benefits in all types of SMA. Open-label studies included patients 2 to 17 years of age with 2 to 5 *SMN2* copies and symptom onset corresponding to types 2 and 3 SMA; these results plus the initial summary of the sham-controlled trial in later-onset patients support the conclusion that nusinersen provides clinical benefits to patients with types 2 and 3 SMA and allow reasonable extrapolation to these populations. Given the invasive nature of nusinersen administration, patients with milder forms of SMA (type 4) may need to weigh potential benefits, risks and discomfort, and relative symptom severity to make individual treatment decisions (*FDA medical review 2016*).

Guidelines

- Consensus guidelines from participants of the International Conference on SMA Standard of Care describe supportive care relating to pulmonary complications, gastrointestinal issues/nutrition, and orthopedics/rehabilitation (*Wang et al 2007*). Key features of supportive care include airway clearance, noninvasive ventilatory support, assessment and treatment of feeding difficulties, nutritional supplementation, posture management, orthotics, and assistive equipment. The guidelines have not been updated to include drug treatment with nusinersen.

SAFETY SUMMARY

- Contraindications
    - None
- Warnings/precautions
    - 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%) nusinersen-treated patients with normal or above normal platelet levels at baseline developed a platelet level below normal, compared to 0 of 28 control patients. No patient had a platelet count < 50,000/mcL and no patient developed a sustained low platelet count despite continued drug exposure.
        - Patients may be at increased risk of bleeding complications. A platelet count and coagulation laboratory testing should be conducted at baseline, prior to each nusinersen dose, and as clinically needed.
    - Renal toxicity
        - Renal toxicity, including potentially fatal glomerulonephritis, has been observed after administration of some antisense oligonucleotides.
        - Nusinersen is present in and excreted by the kidney. In a clinical study, 17 of 51 (33%) nusinersen-treated patients had elevated urine protein, compared to 5 of 25 (20%) control patients. In a group of later-onset SMA patients, 36 of 52 (69%) had elevated urine protein. No elevations in serum creatinine or cystatin C were observed in these studies.
        - Quantitative spot urine protein testing should be conducted at baseline and before each nusinersen dose. If the urinary protein concentration is > 0.2 g/L, repeat testing and further evaluation should be considered.
- Adverse effects
    - In the controlled study in infants with symptomatic SMA, the most common adverse events (AEs) that occurred, in ≥ 20% of nusinersen-treated patients and at least 5% more frequently than in control patients, were lower respiratory infection (43% vs 29%), upper respiratory infection (39% vs 34%), and constipation (30% vs 22%). Serious AEs of atelectasis were more frequent in nusinersen-treated patients than control patients (14% vs 5%).
    - Other reported AEs included teething, upper respiratory tract congestion, aspiration, ear infections, scoliosis, severe hyponatremia, rash, and reduction in growth.
    - In the open-label studies in later-onset patients, the most common AEs included headache (50%), back pain (41%), and post lumbar puncture syndrome (41%).
    - Because patients in the controlled study were infants, AEs that would be verbally reported could not be assessed.
- 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 patients (4%) 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, AEs, or pharmacokinetics.

DOSING AND ADMINISTRATION

Table 4. Dosing and Administration

Drug	Available Formulations	Usual Recommended Dose	Administration Considerations
SPINRAZA (nusinersen)	Injection for intrathecal use	12 mg (5 mL); 4 loading doses (first 3 at 14-day intervals, then a fourth dose 30 days after the third dose); maintenance dosing every 4 months	To be given by, or under the direction of, healthcare professionals experienced in performing lumbar punctures; administered as an intrathecal bolus over 1 to 3 minutes; sedation should be considered as indicated by the clinical condition of the patient; ultrasound or other imaging techniques should be considered to guide administration, particularly in younger patients

SPECIAL POPULATIONS

Table 5. Special Populations

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
SPINRAZA (nusinersen)	No experience; SMA is largely a disease of children and young adults	Safety and effectiveness established for pediatric patients from newborn to 17 years	No data available	No data available	No adequate data on developmental risk associated with use in pregnant women Unknown whether excreted in breast milk; risks and benefits should be considered

CONCLUSION

- Nusinersen is the first medication to be FDA-approved for the treatment of SMA, a serious neuromuscular disease that is the most common genetic cause of infant death and can also affect older children and adults.
- Initial results from randomized trials have demonstrated the efficacy of nusinersen in improving motor function and improving event-free survival, and small single-arm trials provided supportive evidence in several different patient types.
    - A pivotal trial, ENDEAR, was a Phase 3, double-blind, sham-controlled trial enrolling patients 7 months or younger who had an onset of SMA symptoms at ≤ 6 months of age (*Finkel et al 2017, Spinraza dossier 2016*). At the interim analysis, a higher proportion of patients treated with nusinersen had a motor milestone response than those in the control group (41% vs 0%). A co-primary endpoint of event-free survival also favored nusinersen (61%) compared to control (32%).
    - Another Phase 3, double-blind, sham-controlled trial, CHERISH, was conducted in patients aged 2 to 12 years with later-onset SMA (*Biogen Medical Information 2016, Spinraza dossier 2016*). In a pre-planned interim analysis, there was a difference of 5.9 points in the HFMSE at 15 months between the nusinersen and control groups ($p = 0.0000002$). Results for other endpoints were consistent with a favorable response to nusinersen compared to control (specific results not yet reported).
    - Additional open-label, single-arm, Phase 1 and 2 studies offer further support for the use of nusinersen in SMA patients, including patients with symptom onset between 3 weeks and 6 months of age, pre-symptomatic

patients with genetically-diagnosed SMA, and patients aged 2 to 15 years with type 2 or 3 SMA (*Bertini et al 2016, Darras et al 2016, Finkel et al 2016, Spinraza dossier 2016*).

- Nusinersen has generally been well tolerated in clinical trials. Key warnings/precautions include:
  - Thrombocytopenia and coagulation abnormalities – a platelet count and coagulation laboratory testing should be conducted at baseline, prior to each nusinersen dose, and as clinically needed.
  - Renal toxicity – quantitative spot urine protein testing should be conducted at baseline and before each nusinersen dose.
- In the controlled study in infants with symptomatic SMA, the most common AEs that occurred, in ≥ 20% of nusinersen-treated patients and at least 5% more frequently than in control patients, were lower respiratory infection, upper respiratory infection, and constipation. Serious AEs of atelectasis were more frequent in nusinersen-treated patients than control patients (14% vs 5%).
- In conclusion, nusinersen provides the first FDA-approved treatment option for SMA, and has been demonstrated to have beneficial effects on clinically relevant endpoints including achievement of motor milestones and event-free survival. Nusinersen is administered by intrathecal injection in healthcare settings.

APPENDIX

- **Hammersmith Functional Motor Scale – Expanded (HFMSE)** (*Spinraza dossier 2016*)
  - Expanded version of the original 20-item Hammersmith Functional Motor Scale that incorporates 13 items from the Gross Motor Function Measure assessment.
  - Consists of 33 items evaluating the child's ability to perform activities. Each item is scored on a 3-point scale, with a score of 2 for "performs without modification," 1 for "performs with modification/adaptation," and 0 for "unable to perform."
  - The total score can range from 0 (all activities failed) to 66 (all activities achieved).
  - A clinically meaningful change was estimated to be a 3-point change at 6 months (in a previous study of other treatments in patients with type 2 or type 3 SMA).
- **Hammersmith Infant Neurological Examination (HINE)** (*De Sanctis 2016, Spinraza dossier 2016, FDA Medical Review 2016, Together in SMA 2016*)
  - Measures functional ability and achievement of motor milestones.
  - Contains 26 items; total possible score is 78. Healthy-term infants should have a median score ≥ 67 at 3 months and ≥ 70 at 6 months. At 9 or 12 months, scores ≥ 73 are regarded as optimal.
    - Section 1 is based on the neurological exam (postures, cranial nerve function, reflexes, tone, and movements)
    - Section 2 (HINE-2) evaluates development of motor function based on 8 items (head control, sitting, voluntary grasp, ability to kick in supine, rolling, crawling, standing, and walking); each item is scored between 0 and 2 to 4, for a maximum score of 26.
    - Section 3 evaluates the state of behavior (consciousness, social orientation, and emotional state).
- **Six-Minute Walk Test** (*Spinraza dossier 2016*)
  - Evaluates functional exercise capacity by measuring the maximum distance a person can walk in 6 minutes over a 25 meter linear course.
  - Has been accepted by regulatory agencies as a clinically meaningful endpoint in other neurologic disorders.
- **Upper Limb Module (ULM)** (*Spinraza dossier 2016*)
  - Designed to assess upper limb functional abilities in patients with SMA, including young children and patients with severe contractures in the lower limbs.
  - Consists of 9 upper limb performance items that reflect activities of daily living.
  - The total score ranges from 0 to 18 points, with higher scores indicating greater functional abilities.
  - An increase of ≥ 2 points is considered clinically meaningful.
  - A revised version of the ULM consists of 20 upper limb performance items.

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