PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PRSPINRAZATM
(nusinersen injection)

Solution for intrathecal injection 2.4 mg/mL nusinersen as nusinersen sodium

Other drugs for disorders of the musculo-skeletal system

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Submission Control No: 200070

Date of Preparation: June 29, 2017
Date of Revision:
PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

<table>
<thead>
<tr>
<th>Route of Administration</th>
<th>Pharmaceutical Form/Strength</th>
<th>Nonmedicinal Ingredients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intrathecal by lumbar puncture</td>
<td>Solution for intrathecal injection 2.4 mg/mL</td>
<td>sodium dihydrogen phosphate dihydrate, disodium phosphate, sodium chloride, potassium chloride, calcium chloride dihydrate, magnesium chloride hexahydrate, water for injection</td>
</tr>
</tbody>
</table>

INDICATIONS AND CLINICAL USE

SPINRAZA (nusinersen) is indicated for the treatment of 5q Spinal Muscular Atrophy (SMA).

The efficacy and safety data supporting the use of SPINRAZA for the treatment of SMA were from:
- a randomized, controlled trial and an ongoing open-label clinical trial that included patients with infantile-onset SMA
- completed and ongoing open-label clinical trials in children with later-onset SMA and,
- an ongoing open-label clinical trial in presymptomatic infants with genetically diagnosed SMA (see CLINICAL TRIALS).

Knowledge of the disease natural history and the use of management strategies that assist the patient in coping with the manifestations of SMA, which may include decline in motor function, serious respiratory complications and feeding difficulties remain necessary for the overall management of the disease. Treatment with SPINRAZA should only be initiated by healthcare professionals who are experienced in the management of SMA.

There are limited data in patients over the age of 18 years (see CLINICAL TRIALS).

**Adult:** There are limited data from patients over 18 years of age. SPINRAZA has been studied in patients ranging in age from newborn to 19 years (see CLINICAL TRIALS).

**Geriatrics (> 65 years of age):**
There are no data from patients over the age of 65.

CONTRAINDICATIONS
SPINRAZA (nusinersen) is contraindicated in patients with known or suspected hypersensitivity to nusinersen or to any of the ingredients in the formulation or component of the container.

WARNINGS AND PRECAUTIONS

General
The route of administration for SPINRAZA (nusinersen) is intrathecal injection by lumbar puncture and should be administered by healthcare professionals who are experienced in performing lumbar puncture procedures. Patients should be evaluated for the presence of potential contraindications for lumbar puncture (e.g., skin infection near site of lumbar puncture, suspicion of increased intracranial pressure due to a cerebral mass, uncorrected coagulopathy, acute spinal cord trauma), and all necessary precautions should be taken to avoid serious procedural complications (see DOSAGE AND ADMINISTRATION; ADVERSE REACTIONS, Postmarket Adverse Events).

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

In the controlled clinical study of patients with infantile-onset SMA, 6 of 56 (11%) patients treated with SPINRAZA (intrathecal administration) with a normal or above normal baseline level compared to 0 of 28 sham-control patients developed a platelet level that was below the lower limit of normal. No patients developed a platelet count less than 50,000 cells per microliter in this study and no patients developed a sustained low platelet count despite continued drug exposure.

Patients may be at increased risk of bleeding complications due to the risk of thrombocytopenia and coagulation abnormalities with SPINRAZA.

Perform a platelet count and coagulation laboratory testing at baseline and as clinically indicated (see WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests).

Renal
Renal toxicity, including potentially fatal glomerulonephritis, has been observed after intravenous or subcutaneous administration of some antisense oligonucleotides. SPINRAZA is found in high concentrations in the kidney, localized mainly in proximal tubule cells, and is excreted by the kidney (see ACTION AND CLINICAL PHARMACOLOGY).

In the controlled clinical study of infantile-onset SMA patients (mean treatment exposure 7 months), 17 of 51 (33%) patients treated with SPINRAZA (intrathecal injection) developed elevated urine protein relative to baseline, compared to 5 of 25 (20%) sham-control patients. In clinical studies of later-onset SMA patients (mean treatment exposure 34 months), 36 of 52 (69%) developed elevated urine protein. No elevations in serum creatinine or cystatin C were observed.
Conduct quantitative spot urine protein testing (preferably using a first morning urine specimen) at baseline and as clinically indicated. For urinary protein concentration greater than 0.2 g/L, consider repeat testing and further evaluation.

**Cardiovascular**
(See ADVERSE REACTIONS)

**Carcinogenesis and Mutagenesis**
(see TOXICOLOGY).

**Sexual Function/Reproduction**
The effects of SPINRAZA on labor and delivery are not known.

**Special Populations:**

**Pregnant Women:**

There are no data from clinical studies on the use of SPINRAZA during pregnancy in humans and the effects of SPINRAZA on labor and delivery are not known. Because the potential developmental risk associated with the use of SPINRAZA in pregnant women is not known, the use of SPINRAZA during pregnancy is not recommended.

In animal studies administration of nusinersen by subcutaneous injection to mice and rabbits during pregnancy did not have toxic effects on embryo-fetal development (see TOXICOLOGY).

**Nursing Women:**

It is not known if nusinersen is present in human breast milk.

There are no data on the use of SPINRAZA during lactation in humans and the effects of nusinersen on the breastfed infant are not known.

**Pediatrics:**

In repeated dose toxicity studies in juvenile cynomolgus monkeys, following intrathecal administration of nusinersen (0.3, 1, or 3 mg/dose for 14 weeks or 0.3, 1, 3 or 4 mg/dose for 53 weeks) or vehicle control, brain histopathology (neuronal vacuolation and necrosis/cellular debris in the hippocampus) was observed at the mid- (1 mg/dose) and high doses (3 mg or 4 mg/dose), specifically in the inferior region of the hippocampus. Possible neurobehavioral deficits were observed on a learning and memory test at the high dose in the 53-week monkey study. The no-observed adverse effect level (NOAEL) 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. The clinical significance of these observations in monkeys is not known.

**Monitoring and Laboratory Tests**
Conduct the following laboratory tests at baseline and as clinically indicated:
- Platelet count (see WARNINGS AND PRECAUTIONS, Hematologic)
• Prothrombin time; activated prothrombin time (see WARNINGS AND PRECAUTIONS, Hematologic)
• Quantitative spot urine testing (see WARNINGS AND PRECAUTIONS, Renal)

ADVERSE REACTIONS

Adverse Drug Reaction Overview
The safety of SPINRAZA (nusinersen) was evaluated in infants with SMA in an interim analysis of a phase 3 randomized, double-blind, sham-controlled study of symptomatic infants (1 to 7 months of age at study entry, SPINRAZA n=80, control n=41); an ongoing open-label phase 2 study in symptomatic infants (1 to 8 months of age at study entry, n=20); and, an ongoing open-label phase 2 study in pre-symptomatic infants genetically diagnosed with SMA (8 to 42 days old at study entry, n=17). The safety of SPINRAZA in patients with later-onset SMA was evaluated in completed and ongoing open-label phase 1 and phase 2 studies of patients who were 2 to 17 years of age at study entry (n=56).

A total of 173 patients were exposed to SPINRAZA in the clinical trials for a total duration of 6 to 1536 days (median 324 days); 120 patients were exposed for at least 6 months and 83 were exposed for at least 12 months. In the controlled study in symptomatic infants, 41 patients were exposed to SPINRAZA for at least 6 months and 19 patients were exposed for at least 12 months. The nature of the adverse events reported during all clinical trials suggests that the majority may have been related to SMA disease or the lumbar puncture procedure.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

In Study 1, the randomized, double-blind, controlled clinical trial in patients with infantile-onset SMA, 80 patients received SPINRAZA (12 mg intrathecal injection by lumbar puncture, median exposure 187.5 days) and 41 patients received sham-control (dermal puncture, median exposure 129 days). Baseline disease characteristics were similar in both groups, except that the SPINRAZA group had a greater proportion of patients at baseline with (SPINRAZA vs sham-control) paradoxical breathing (89% vs 66%), pneumonia or respiratory symptoms (35% vs 22%), swallowing or feeding difficulties (51% vs 29%) and requirement for non-invasive respiratory support (26% vs 15%).

The most common treatment emergent adverse events in both groups were respiratory or infection adverse events (Table 1). Because the patients in this study were infants, adverse reactions that are verbally reported (e.g., post-lumbar puncture syndrome, headache) could not be assessed in these patients.

Serious adverse events occurred in 70% of patients in the SPINRAZA group and 80% of patients in the sham-control group. The most common serious adverse events in both groups were
respiratory events (58% SPINRAZA vs 63% sham-control) or infection adverse events (50% SPINRAZA vs 37% sham-control). Serious adverse events of atelectasis were more frequent in patients that received SPINRAZA (14%) than in patients that received the sham-control (5%).

Table 1: Treatment Emergent Adverse Events\(^1\) Occurring in at Least 5% of Patients Treated with SPINRAZA\(^2\) or Sham-control and More Frequently in Patients Treated with SPINRAZA in the controlled clinical trial in patients with infantile-onset SMA

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Preferred term</th>
<th>Control N=41 n (%)</th>
<th>SPINRAZA N=80 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any adverse event</td>
<td>38 (93)</td>
<td>72 (90)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Constipation</td>
<td>23 (56)</td>
<td>46 (58)</td>
</tr>
<tr>
<td></td>
<td>Teething</td>
<td>9 (22)</td>
<td>24 (30)</td>
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<tr>
<td></td>
<td></td>
<td>3 (7)</td>
<td>11 (14)</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Upper respiratory tract congestion</td>
<td>34 (83)</td>
<td>55 (69)</td>
</tr>
<tr>
<td></td>
<td>Aspiration</td>
<td>1 (2)</td>
<td>5 (6)</td>
</tr>
<tr>
<td></td>
<td>Hypoxia</td>
<td>1 (2)</td>
<td>4 (5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 (5)</td>
<td>6 (8)</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>Upper respiratory tract infection</td>
<td>29 (71)</td>
<td>57 (71)</td>
</tr>
<tr>
<td></td>
<td>Pneumonia</td>
<td>9 (22)</td>
<td>20 (25)</td>
</tr>
<tr>
<td></td>
<td>Nasopharyngitis</td>
<td>6 (15)</td>
<td>17 (21)</td>
</tr>
<tr>
<td></td>
<td>Bronchiolitis</td>
<td>4 (10)</td>
<td>14 (18)</td>
</tr>
<tr>
<td></td>
<td>Respiratory tract infection</td>
<td>3 (7)</td>
<td>8 (10)</td>
</tr>
<tr>
<td></td>
<td>Viral infection</td>
<td>2 (5)</td>
<td>7 (9)</td>
</tr>
<tr>
<td></td>
<td>Oral candidiasis</td>
<td>2 (5)</td>
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<tr>
<td></td>
<td>Pneumonia viral</td>
<td>3 (7)</td>
<td>6 (8)</td>
</tr>
<tr>
<td></td>
<td>Bronchitis</td>
<td>1 (2)</td>
<td>6 (8)</td>
</tr>
<tr>
<td></td>
<td>Ear infection</td>
<td>0</td>
<td>5 (6)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 (2)</td>
<td>4 (5)</td>
</tr>
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<td>Skin and subcutaneous tissue disorders</td>
<td>Dermatitis diaper</td>
<td>13 (32)</td>
<td>21 (26)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 (5)</td>
<td>6 (8)</td>
</tr>
<tr>
<td>Muscle and connective tissue disorders</td>
<td>Scoliosis</td>
<td>4 (10)</td>
<td>11 (14)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 (2)</td>
<td>4 (5)</td>
</tr>
<tr>
<td>Metabolism and nutrition</td>
<td>Weight gain poor</td>
<td>10 (24)</td>
<td>13 (16)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 (5)</td>
<td>5 (6)</td>
</tr>
</tbody>
</table>

\(^1\)Presented as MedDRA preferred terms under the MedDRA system organ class (SOC) (MedDRA Version 18.1)

\(^2\)Administered as 12 mg/dose, four loading doses on Days 1, 15, 29 and 64, followed by two maintenance doses administered every 4 months (Days 183 and 302)

In the open-label studies that included 56 patients with later-onset SMA (Study 4, 5, 6, and 7) the most common treatment emergent adverse events reported in more than 10% of the SPINRAZA-treated patients were headache (50%), upper respiratory tract infection (48%), post-lumbar-puncture syndrome (41%), back-pain (41%), pyrexia (29%), nasopharyngitis (29%), scoliosis (27%), vomiting (21%), nausea (18%), puncture site pain (18%), joint contracture (18%), viral infection (16%), gastroenteritis viral (14%), pharyngitis streptococcal (14%), oropharyngeal pain (14%), gastroenteritis, constipation (13%), laceration (13%), rhinorhea (11%), cough (11%), procedural pain (11%). The majority of adverse events of headache, post-lumbar puncture
syndrome, back pain, puncture site pain and vomiting were reported within 72 hours of lumbar puncture procedures.

**QTc interval abnormalities**
In the controlled clinical study of 121 patients with infantile-onset SMA, among patients with normal baseline QTc values, two subjects treated with SPINRAZA had a post-baseline QTc value >500 msec and a >60 msec increase from baseline. There were no patients with an adverse event of QTc prolongation and there was no increase in the incidence of cardiac adverse events associated with delayed ventricular repolarization in patients treated with SPINRAZA compared to the sham control.

**Effect on growth**
A reduction in growth, as measured by height, was suggested in the controlled clinical trial in patients with infantile-onset SMA treated with SPINRAZA. It is not known if any effect of SPINRAZA on growth would be reversible upon discontinuation of treatment.

**Rash**
Cases of rash were reported in the controlled clinical trial in patients with infantile-onset SMA. One patient developed painless lesions on the forearm, leg and foot, over an 8-week period 8 months after starting treatment with SPINRAZA. The lesions were initially red macular skin lesions that ulcerated and scabbed over in 4 weeks. The patient continued to have recurring painless ulcerative lesions in acral distribution. A second patient developed red macular lesions on the hands 10 months after starting treatment with SPINRAZA, which resolved over a period of 3 months. In both cases there was spontaneous resolution of the rash while the patients continued to receive SPINRAZA.

**Hyponatremia**
One patient treated with SPINRAZA in an open-label study including patients with infantile onset SMA had a serious adverse event of hyponatremia requiring daily salt supplementation for 14 months.

**Immunogenicity**
The immunogenic response to nusinersen was determined by the evaluation of anti-drug antibodies (ADA) in patients with baseline and post-baseline plasma samples (n=126). Overall, the incidence of ADAs were low, with 4 patients developing treatment-emergent ADAs, of which 2 were transient and 2 were considered to be persistent. There were insufficient data to evaluate the effect of ADAs on clinical response, adverse events, or the pharmacokinetic profile of nusinersen.

**Post-market Adverse Events**
Adverse events including serious infection, associated with the lumbar puncture procedure used for administration of SPINRAZA, have occurred in the post market setting. SPINRAZA should be administered by healthcare professionals who are experienced in performing lumbar puncture procedures (see WARNINGS AND PRECAUTIONS, General; DOSAGE AND ADMINISTRATION).

**DRUG INTERACTIONS**
No clinical studies of interactions with other medicines have been performed. Nusinersen is metabolized via nuclease and not by the cytochrome P450 (CYP450) system. 

*In vitro* studies indicated that nusinersen is not an inducer or inhibitor of CYP450 mediated metabolism.

*In vitro* studies indicated that the likelihood for interactions with nusinersen due to competition with or inhibition of transporters is low.

The co-administration of other intrathecal agents with SPINRAZA has not been evaluated and the safety of these combinations is not known.

**DOSAGE AND ADMINISTRATION**

**Dosing Considerations**
SPINRAZA (nusinersen) is only for intrathecal use by lumbar puncture. SPINRAZA should not be administered by intravenous, intramuscular, subcutaneous or epidural routes.

Treatment should be administered by health care professionals experienced in performing lumbar punctures.

SPINRAZA has not been studied in patients with renal impairment.

SPINRAZA has not been studied in patients with hepatic impairment. SPINRAZA is not metabolized via the cytochrome P450 enzyme system in the liver, therefore dosage adjustment is unlikely to be required in patients with hepatic impairment (see DRUG INTERACTIONS and ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions).

**Recommended Dose**
The recommended dose is 12 mg (5 mL).

**Loading doses**
Initiate treatment with 4 loading doses. The first 3 loading doses should be administered at 14-day intervals (e.g., Day 0, Day 14, Day 28). The fourth loading dose should be administered approximately 30 days after the third loading dose (e.g., Day 63).

**Maintenance doses**
Following the fourth loading dose, a maintenance dose should be administered once every 4 months.

**Missed Dose**
If a loading dose is delayed or missed SPINRAZA should be administered as soon as possible, with at least 14 days between doses, and dosing should continue at the prescribed frequency.

If a maintenance dose is delayed or missed SPINRAZA should be administered as soon as possible and dosing should continue at the prescribed frequency.

**Administration**

**Preparation of dose**
1. The vial should be taken out of the refrigerator and allowed to warm to room temperature (25°C/77°F) without using external heat sources, prior to administration. The solution must be visually inspected prior to use. Only clear and colorless solutions, free from particles, can be used. Do not administer SPINRAZA if visible particles are observed or if the solution in the vial is discolored. Do not use external filters.

2. Aseptic technique must be used when preparing and administering SPINRAZA.

3. Just prior to administration insert the syringe needle into the vial through the center of the over-seal and withdraw 12 mg (5 mL) of SPINRAZA from the vial into the syringe. SPINRAZA must not be diluted. If a vial remains unopened and the solution has not been used, it should be returned back to the refrigerator.

Administration of dose
1. Sedation may be required to administer SPINRAZA, as indicated by the clinical condition of the patient.
2. Ultrasound (or other imaging techniques) may be considered to guide intrathecal administration of SPINRAZA, particularly in younger patients.
3. Prior to administration, removal of 5 mL of cerebral spinal fluid is recommended.
4. Administer SPINRAZA as an intrathecal bolus injection over 1 to 3 minutes, using a spinal anesthesia needle. Do not administer SPINRAZA in areas of the skin where there are signs of infection or inflammation.
5. Once drawn in to the syringe, if the solution is not used within 6 hours, it must be discarded.

OVERDOSAGE
No cases of overdose associated with adverse reactions were reported in clinical studies.

In case of overdose with SPINRAZA the patient should be advised to seek medical attention if they experience any signs or symptoms of adverse reactions.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action
SPINRAZA (nusinersen) is an antisense oligonucleotide (ASO) specifically designed to treat SMA, an autosomal recessive progressive neuromuscular disease, caused by mutations in the chromosome 5q. These mutations lead to loss of function of the survival motor neuron 1 (SMN1) gene, resulting in deficiency of SMN protein. The SMN2 gene also produces SMN protein but at low levels. In patients with SMA, fewer SMN2 gene copies are associated with earlier age of onset and increased severity of symptoms.

SPINRAZA binds to a specific site in the SMN2 pre-messenger ribonucleic acid (pre-mRNA) to increase the proportion of exon 7 inclusion in SMN2 messenger ribonucleic acid (mRNA) transcripts made, which can be translated into the functional full length SMN protein.

Pharmacodynamics
Autopsy samples from treated infants had higher levels of SMN2 messenger ribonucleic acid (mRNA) containing exon 7 in the thoracic spinal cord compared to untreated SMA infants.
Pharmacokinetics
Single- and multiple-dose pharmacokinetics of nusinersen, administered via intrathecal injection, were determined in pediatric patients diagnosed with SMA.

Absorption: Intrathecal injection of nusinersen 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 Tmax values ranged from 1.7 to 6.0 hours. Mean plasma Cmax and AUC values increased approximately dose proportionally over the evaluated dose range up to 12 mg. There is no accumulation in plasma exposure measures (Cmax and AUC) after multiple doses.

Distribution: Autopsy data from patients (n=3) showed that following intrathecal administration, nusinersen was broadly distributed within the CNS and peripheral tissues such as skeletal muscle, liver, and kidney.

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

Elimination: The mean terminal elimination half-life is estimated at 135 to 177 days in CSF and 63 to 87 days in plasma. Following slow metabolism in tissues, the primary route of elimination is likely by urinary excretion of nusinersen and its chain-shortened metabolites. During the first 24 hours after dosing, only 0.5% of the administered dose was recovered in urine.

Special Populations and Conditions:

Gender: Population pharmacokinetic analysis showed that gender does not affect the pharmacokinetics of nusinersen.

Renal and Hepatic Insufficiency: The pharmacokinetics of nusinersen in patients with renal impairment or hepatic impairment have not been studied.

STORAGE AND STABILITY

Store refrigerated at 2°C to 8°C (36°F to 46°F). 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 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 and secondary packaging should not exceed 30 hours, at a temperature that does not exceed 25°C (77°F).

Once in the syringe, if the solution is not used within 6 hours, it must be discarded.

Discard any unused solution left in a vial.
DOSAGE FORMS, COMPOSITION AND PACKAGING

Single-use solution for intrathecal injection containing 5 mL of a 2.4 mg/mL clear and colorless solution of nusinersen.

**Composition**
SPINRAZA is formulated at a pH of approximately 7.2 and contains:

- Artificial cerebral spinal fluid contents per 5 mL;
- Sodium dihydrogen phosphate dihydrate (0.25 mg),
- Disodium phosphate (0.49 mg),
- Sodium chloride (45.83 mg),
- Potassium chloride (1.12 mg),
- Calcium chloride dihydrate (1.03 mg),
- Magnesium chloride hexahydrate (0.82 mg)
- Water for Injection

Sodium hydroxide and hydrochloric acid may be used for pH adjustment.

**Packaging**
SPINRAZA is supplied as 5mL in a Type I vial with bromobutyl rubber stopper and an aluminium over-seal and plastic cap. Pack size: one vial per carton.
PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: nusinersen

Molecular formula and molecular mass: The molecular formula of SPINRAZA is C_{234}H_{323}N_{61}O_{128}P_{17}S_{17}Na_{17} and the molecular weight is 7501.0 amu

Structural formula:

Physicochemical properties: Nusinersen is a fully modified 2'-O-2-methoxyethyl antisense oligonucleotide designed to bind to a specific sequence in the intron downstream of Exon 7 of the SMN2 transcript. SPINRAZA is a sterile, preservative-free solution that contains 2.4 mg/mL nusinersen in artificial cerebral spinal fluid. SPINRAZA contains 12.6 mg nusinersen sodium equivalent to 12 mg nusinersen free acid in 5 mL per vial.

pH of approximately 7.2.

CLINICAL TRIALS

Study demographics and trial design
## Table 2 - Summary of patient demographics for clinical trials

<table>
<thead>
<tr>
<th>Study #</th>
<th>Trial design</th>
<th>Dosage and duration(^1)</th>
<th>Study subjects (n = number)</th>
<th>Population studied</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 1 (ENDEAR; CS3B)</td>
<td>Phase 3, Randomized, double-blind, multiple-dose, sham-procedure controlled in subjects with symptomatic infantile-onset SMA [ongoing]</td>
<td>12 mg scaled equivalent dose or sham-procedure (2:1) Loading dose: Days 1, 15, 29, 64 Maintenance dose: Days 183 and 302</td>
<td>121</td>
<td>Most likely to develop Type I SMA Median age at symptom onset 8 weeks (range 1 to 20 weeks) SMN2 gene copies: 2 (118), 3 (1), unknown (2) Median age at first dose: 175 days (range 30 to 262 days) Gender: - 45% male - 55% female</td>
</tr>
<tr>
<td>Study 2 (CS3A)</td>
<td>Phase 2, open label, multiple-dose in subjects with symptomatic infantile-onset SMA [ongoing]</td>
<td>Cohort 1: 6 mg scaled equivalent loading dose and 12 mg maintenance dose Cohort 2: 12 mg scaled equivalent loading dose and 12 mg maintenance dose Loading dose: Days 1, 15, and 85 Maintenance dose: Day 253 and every 4 months thereafter.</td>
<td>20</td>
<td>Most likely to develop Type I or Type II SMA Median age at symptom onset 56 days (range: 21 to 154 days) SMN2 gene copies: 2 (17), 3 (2), unknown (1) Median age at enrollment: 155 days (range 36 to 210) Gender: - 60% male - 40% female</td>
</tr>
<tr>
<td>Study 3 (NURTURE ; CS5; SM201)</td>
<td>Ongoing, open label study in pre symptomatic infants genetically diagnosed with SMA [ongoing]</td>
<td>12 mg scaled equivalent loading and maintenance doses of nusinersen on day 1, 15, 29, 64, 183, 302, 421, 540, 659, and 778.</td>
<td>17 enrolled</td>
<td>Most likely to develop Type I or II SMA. SMN2 gene copies: 2 (12), 3 (5) Gender: - 65% male - 35% female</td>
</tr>
<tr>
<td>Study #</td>
<td>Trial design</td>
<td>Dosage and duration¹</td>
<td>Study subjects (n = number)</td>
<td>Population studied</td>
</tr>
<tr>
<td>-----------</td>
<td>------------------------------------------------------------------------------</td>
<td>-----------------------</td>
<td>----------------------------</td>
<td>------------------------------------------------------------------</td>
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<tr>
<td>Study 4</td>
<td>(CS2) Phase 1, open-label, dose-escalation, multiple dose in subjects with symptomatic later-onset SMA</td>
<td>3, 6, 9, and 12 mg nusinersen. 2 doses on days 1 and 85 (9mg cohort) or 3 doses on days 1, 29, and 85 (3, 6 and 12 mg cohorts).</td>
<td>56</td>
<td>Diagnosed with Type II or III SMA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Median age at symptom onset: 14 months (range: 3 to 60 months)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>SMN2 gene copies: 2 copies (1), 3 copies (46), 4 copies (8), 5 copies (1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Median age at first dose: 6.15 years (range 2 to 15.9 years)</td>
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<tr>
<td></td>
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<td>Gender:</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>- 46% male</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- 54% female</td>
</tr>
<tr>
<td>Study 5</td>
<td>(CS12) Phase 1, open-label, multiple-dose, single-arm in subjects with symptomatic later-onset SMA [ongoing extension for patients completing Study CS2, or Studies CS1 and CS10]</td>
<td>12 mg scaled equivalent loading and maintenance doses of nusinersen on days 1, 169, 351, and 533</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study 6</td>
<td>(CS1) Phase 1, open-label, escalating dose in subjects with symptomatic later-onset SMA</td>
<td>single dose of 1, 3, 6, or 9 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study 7</td>
<td>(CS10) Phase 1, open-label, single dose in subjects with symptomatic later-onset SMA</td>
<td>single dose of 6 or 9 mg</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

¹ Intrathecal administration

The efficacy of SPINRAZA (nusinersen) was demonstrated in the interim analysis of a phase 3, randomized, double-blind, sham-procedure controlled clinical trial in symptomatic patients with infantile-onset SMA (Study 1), and supported by ongoing and completed open-label clinical trials conducted in patients with infantile-onset SMA, patients with later-onset SMA, and patients with presymptomatic genetically diagnosed SMA (Study 2, 3, 4 and 5).

**Clinical Trial in Infantile-Onset SMA**

This study was a phase 3, multicenter, randomized, double-blind, sham-procedure controlled study in 121 symptomatic infants ≤ 7 months of age at the time of first dose or sham procedure, diagnosed with SMA (symptom onset before 6 months of age). Patients included in the study were deemed most likely to develop type I SMA. Patients were randomized 2:1 to either SPINRAZA or sham-control. Patients randomized to the SPINRAZA group received 4 loading doses of 12 mg nusinersen intrathecal injection, administered by lumbar puncture, on Days 1, 15, 29 and 64, followed by maintenance doses administered at 4-month intervals on Days 183 and 302. In the sham-control group patients received a dermal puncture at all scheduled dosing visits. At the interim analysis patients in the SPINRAZA group received a median of 4 doses (median exposure 187.5 days) and patients in the sham-control group had a median of 4 sham-control procedures (median exposure 129 days).
The planned interim analysis was conducted based on patients who received at least 1 treatment during the study and completed at least 183 days of treatment, died or withdrew. At the time of the interim analysis 121 patients received treatment in the study (SPINRAZA n=80, sham-control n=41). A total of 78 patients had completed at least 183 days of treatment, died or withdrew at the time of the interim analysis and were included in the Interim Efficacy Set for the primary endpoint analysis (SPINRAZA n=51, sham-control n=27). In the Interim Efficacy Set, 45% of patients were male and 55% were female; 86% were Caucasian, 2% were Black and 3% were Asian. Age at first treatment in the study ranged from 30 to 262 days, with a median age of 181 days. Baseline demographics were balanced between the treatment groups, with the exception of age at first treatment, which was lower in the SPINRAZA group compared to the sham-control group (median age: 175 days vs 205 days). Both treatment groups were similar with respect to gestational age (median 39 weeks), birth weight (median 3.35 kg), disease duration (median 13.4 weeks) and SMN2 copy number (2 copies in 96% to 98% of patients). There were baseline imbalances related to SMA symptoms (see ADVERSE REACTIONS), including an imbalance in age of symptom onset; 88% of patients in the SPINRAZA group compared to 74% in the sham-control group had onset of symptoms within the first 12 weeks of life.

The primary endpoint assessed at the time of interim analysis was the proportion of patients who were treatment responders based on achieving a pre-specified level of improvement in motor milestones evaluated by Section 2 of the Hammersmith Infant Neurologic Exam (HINE). Section 2 of the HINE was used to evaluate achievement of motor milestones in 7 categories (head control, sitting, ability to kick in supine position, rolling, crawling, standing and walking), with 3 to 5 progressively more difficult items for each milestone category. Depending on the milestone the maximum scores for each category ranges from 2 to 4 points. A treatment responder was defined as any patient having at least a 2-point increase [or maximal score of 4] in ability to kick, OR at least a 1-point increase in the motor milestones of head control, rolling, sitting, crawling, standing or walking. Improvement in more categories of motor milestones than worsening was required to be considered a responder for the primary analysis. Patients who died or withdrew were included in the Interim Efficacy Set and considered non-responders. In the Interim Efficacy Set, a greater percentage of patients in the SPINRAZA group compared to the sham-control group met the criteria for motor milestone responder (41% vs 0%, p<0.0001, 95% CI: 18%, 61%). A descriptive presentation of the distribution of the net change from baseline in the total motor score for Section 2 of the HINE is shown in Figure 1.
Figure 1. Distribution of the net change from baseline in HINE total motor milestone score by percent of patients 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.

Additional endpoints evaluated at the interim analysis included but were not limited to: the Children’s Hospital of Philadelphia Infant Test for Neuromuscular Disease (CHOP-INTEND), which evaluates muscle strength and function in infants with SMA (neck, trunk, proximal, and distal limb strength); assessment of event-free survival (time to permanent ventilation or death); overall survival; proportion of patients requiring permanent ventilation; annualized rate of hospitalization; and, annualized rate of serious respiratory infections. As specified by the statistical analysis plan for the study, formal statistical testing was not conducted at the interim analysis for these endpoints. A descriptive summary of results for these endpoints is presented in Table 3.

Table 3: Preliminary results for additional endpoints analyzed at the interim analysis of the randomized control clinical trial in patients with infantile-onset SMA

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Analysis set</th>
<th>Sham-control</th>
<th>SPINRAZA</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHOP-INTEND</td>
<td>IES¹</td>
<td>N=27</td>
<td>N=51</td>
</tr>
<tr>
<td>Improvement from baseline ≥ 4 points, n (%)</td>
<td></td>
<td>1 (4)</td>
<td>33 (65)</td>
</tr>
<tr>
<td>Worsening from baseline ≥ 4 points, n (%)</td>
<td></td>
<td>12 (44)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Event-free survival</td>
<td>ITT²</td>
<td>N=41</td>
<td>N=80</td>
</tr>
<tr>
<td>Proportion of patients that died or required permanent ventilation³, n (%)</td>
<td></td>
<td>20 (49)</td>
<td>27 (34)</td>
</tr>
<tr>
<td>Hazard ratio⁵</td>
<td></td>
<td></td>
<td>0.71</td>
</tr>
<tr>
<td>Risk reduction</td>
<td></td>
<td></td>
<td>29%</td>
</tr>
<tr>
<td>Proportion of patients that died, n (%)</td>
<td>ITT</td>
<td>N=41</td>
<td>N=80</td>
</tr>
<tr>
<td>Hazard ratio</td>
<td></td>
<td>13 (32)</td>
<td>12 (15)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.44</td>
</tr>
<tr>
<td>Endpoint</td>
<td>Analysis set</td>
<td>Sham-control</td>
<td>SPINRAZA</td>
</tr>
<tr>
<td>----------</td>
<td>--------------</td>
<td>--------------</td>
<td>----------</td>
</tr>
<tr>
<td>Risk reduction</td>
<td></td>
<td></td>
<td>56%</td>
</tr>
<tr>
<td>Proportion of patients requiring permanent ventilation, n (%)</td>
<td>ITT</td>
<td>N=41 9 (22)</td>
<td>N=80 15 (19)</td>
</tr>
<tr>
<td>Hazard ratio</td>
<td></td>
<td></td>
<td>0.90</td>
</tr>
<tr>
<td>Risk reduction</td>
<td></td>
<td></td>
<td>10%</td>
</tr>
<tr>
<td>Unadjusted annualized rate(^6) of hospitalization</td>
<td>IES</td>
<td>N=27</td>
<td>N=51</td>
</tr>
<tr>
<td>Unadjusted annualized rate of serious respiratory adverse events</td>
<td>IES</td>
<td>N=27</td>
<td>N=51</td>
</tr>
</tbody>
</table>

1 IES Interim Efficacy Set, defined as all randomized patients that received at least 1 dose of study medication and had completed at least 183 days of treatment, died or withdrew.
2 ITT Intent to Treat Population, defined as all randomized patients that received at least 1 dose of study medication. Baseline demographics and disease history were similar in the ITT Population and IES.
3 Death or permanent ventilation events were events confirmed by the Endpoint Adjudication Committee.
4 Permanent ventilation was defined as ventilation required ≥16 hours/day continuously for >21 days in the absence of an acute reversible event OR tracheostomy.
5 Hazard ratio using a Cox proportional hazards model adjusted for each patient’s disease duration at screening.
6 Due to the longer duration of observation in the SPINRAZA group, unadjusted annualized rates (for hospitalization and serious respiratory events) were compared.

### Ongoing and completed open-label clinical trials
The results of the controlled trial in infantile-onset SMA patients were supported by data from completed and ongoing phase 1 and phase 2 open-label, uncontrolled trials conducted in symptomatic patients with infantile-onset SMA (n=20, age range 36 days to 210 days at first dose); in patients with later-onset SMA (n=56, age range 2 to 15 years at first dose); and, in presymptomatic genetically diagnosed patients (n=17, age range 8 to 42 days at first dose). Most of the patients included in these studies had or were likely to develop type I, type II or type III 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, when considering the number of SMN2 gene copies of patients enrolled in the studies and the disease natural history. When treatment with SPINRAZA was initiated prior to symptom onset in patients with genetically diagnosed SMA, patients achieved milestones unexpected in type I SMA and more consistent with normal development. It is not known whether ongoing, continuous treatment with SPINRAZA will be required to maintain or prevent loss of motor function that is achieved during treatment.

### TOXICOLOGY
In repeat-dose toxicity studies (14-weeks and 53-weeks) intrathecal administration of nusinersen to juvenile cynomolgus monkeys resulted in transient deficits in lower spinal reflexes which occurred at the highest dose levels in each study (3 or 4 mg per dose; equivalent to 30 or 40 mg per IT dose in patients). These effects were observed within several hours post-dose and generally resolved within 48 hours. Neuronal vacuolation and necrosis/cellular debris in the
hippocampus were also observed at the mid- and high doses (see WARNINGS AND PRECAUTIONS, Pediatrics).

Reproductive toxicology studies were conducted using subcutaneous administration of SPINRAZA in mice and rabbits. No impact on male or female fertility, or embryo-fetal development was observed.

**Carcinogenicity and Mutagenicity**
Long-term carcinogenicity studies have not been conducted.

SPINRAZA demonstrated no evidence of genotoxicity, in *in vitro* assays (Ames and chromosomal aberration in CHO cells) or in *in vivo* assays (mouse micronucleus).
REFERENCES


READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

SPINRAZA
nusinersen injection

Read this carefully before you or your child start receiving SPINRAZA and before each dose. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about you or your child’s medical condition and treatment and ask if there is any new information about SPINRAZA. Keep this leaflet. You may need to read it again.

What is SPINRAZA used for?
SPINRAZA is used to treat a genetic disease called 5q Spinal Muscular Atrophy (SMA). SMA is caused by a problem with the 5q chromosome. This problem leads to a shortage of a particular protein called survival motor neuron (SMN). The shortage of SMN protein results in the loss of nerve cells in the spine that leads to weakness of the muscles in the shoulders, hips, thighs and upper back. It may also weaken the muscles used for breathing and swallowing.

SPINRAZA may be given to children, adolescents or adults:
• There is limited experience of SPINRAZA in people over 18 years of age.
• There is no experience of SPINRAZA in people over 65 years of age.

How does SPINRAZA work?
SPINRAZA is one of a group of medicines called anti-sense oligonucleotides (ASO). SPINRAZA works by helping the body to produce more of the SMN protein that people with SMA need. This may reduce the loss of nerve cells and improve muscle strength.

What are the ingredients in SPINRAZA?
Medicinal ingredients: nusinersen
Non-medicinal ingredients: calcium chloride dihydrate, disodium phosphate, magnesium chloride hexahydrate, potassium chloride, sodium chloride, sodium dihydrogen phosphate dihydrate, water for injection. Sodium hydroxide and hydrochloric acid may be used for pH adjustment.

SPINRAZA comes in the following dosage forms:
Single-use solution in a vial for intrathecal injection containing 5 mL of a 12 mg / 5 mL (2.4 mg / mL) clear and colorless solution of nusinersen. Pack size: one vial per carton.

Do not use SPINRAZA if:
• You or your child has or may have an allergy or hypersensitivity to nusinersen or to any of the ingredients in the formulation or component of the container.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you are given SPINRAZA. Talk about any health conditions or problems you may have.
Warnings you should know about:

Lumbar puncture
• There are known reasons why you or your child should not have a lumbar puncture. These may include:
  o a skin infection near site of lumbar puncture
  o the possibility that you or your child has a brain tumour and increased pressure in the skull
  o uncontrolled problems with blood clotting
  o injury or damage to the spinal cord (only short duration and not ongoing)

Pregnancy, breastfeeding and fertility
There is no experience of the use of SPINRAZA in pregnant women. Ask your doctor for advice about taking SPINRAZA if you:
• are pregnant
• breast-feeding
• think you may be pregnant or are planning to have a baby.

Blood clotting problems and risk of bleeding
After receiving medicines similar to SPINRAZA, some patients had:
• abnormal blood clotting
• abnormal and/or severely low levels of platelets (blood cells responsible for stopping bleeding).

In a SPINRAZA clinical trial, some patients had lower than normal levels of platelets. The lower levels of platelets came and went and the patients did not have abnormal blood clotting.

You may be at risk of bleeding complications while you are taking SPINRAZA. Your doctor will monitor your blood clotting by testing your blood. You will be tested before starting treatment with SPINRAZA and any other time your doctor thinks is necessary.

Risk of kidney damage
After receiving medicines similar to SPINRAZA, some patients had:
• higher levels of protein in their urine
• an increased risk of toxicity in the kidneys
• inflammation of the kidneys, which has caused death.

In a SPINRAZA clinical trial, some patients had higher levels of protein in their urine. SPINRAZA was also found in high concentrations in the kidneys. SPINRAZA leaves the body (is excreted) through the kidneys. It is important that your kidneys work well while you are taking SPINRAZA.

Your doctor will monitor how your kidneys are working by testing your urine. Your urine will be tested before you start treatment with SPINRAZA and any other time your doctor thinks is necessary.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.
At this time, there are no known medicines that interact with SPINRAZA. It is unknown if SPINRAZA can be used safely with other drugs that are administered into the spine (intrathecal).

**How SPINRAZA is given:**
- SPINRAZA is given by injection to the lower back.
- This injection is called a lumbar puncture and is done by inserting a needle in the space around the spinal cord.
- This will be done by a healthcare provider experienced in doing lumbar punctures.
- The injection will take 1 to 3 minutes
- You or your child may also be given a medicine to make you relax or sleep during the injection.
- Ask your health care provider, if you have any questions about how SPINRAZA is given.

Your doctor will tell you how long you or your child needs to keep receiving SPINRAZA. Don’t stop treatment with SPINRAZA unless your doctor tells you to.

**Usual dose:**
The dose of SPINRAZA is 12 mg. You or your child will receive SPINRAZA based on the schedule below:

- The first 3 doses of SPINRAZA will be administered 14 days apart: on Day 0, Day 14 and Day 28.
- The 4th dose will be administered about a month later, for example on Day 63.
- And then once every 4 months.

**Overdose:**
There is no experience with overdose with SPINRAZA.

If you think you have been given too much SPINRAZA, contact your healthcare professional immediately, even if there are no symptoms.

**Missed Dose:**
If you or your child is unable to receive SPINRAZA as planned, speak with your doctor to ensure that SPINRAZA can be given as soon as possible.

**What are possible side effects from using SPINRAZA?**

Like all medicines, SPINRAZA can cause side effects, although not everybody gets them. Contact your doctor or nurse if you notice any of these side effects. Do not try to treat them yourself.

When SPINRAZA was tested in clinical trials, most side effects seemed to be:
- continued symptoms of the disease (SMA), such as:
  - breathing problems, muscle weakness, joint and bone problems, or digestive problems
  - sinus and/or throat infections, colds
  - lung infections like bronchitis and pneumonia
- side effects of the lumbar puncture:
The side effects reported that were likely continued symptoms of the disease included:

- Chest infections (such as pneumonia)
  - wheezing, shortness of breath, chest pain, feeling tired, coughing - sometimes with mucus
- Constipation
- Cough
- Curving of the back or spine (scoliosis)
- Diarrhea
- Difficulty breathing or being unable to breathe
  - signs may include rapid or shallow breathing, an increase in heart rate, and a bluish-tinge of the skin, fingertips or lips
  - may be caused by a collapsed lung or part of a lung
- Difficulty swallowing or being unable to swallow
- Ear infection leading to pain or loss of balance
- Feeling nauseous or throwing up
- Fever
- Heart-burn
- Infections of the nose, throat or upper airways
  - blocked, stuffy or runny nose, sneezing and coughing, a sore or scratchy throat and watery or itchy eyes
- Pain
- Permanent shortening of a muscle or joint
- Rash on forearms, legs, feet, hands
- Reduction in growth
- Stiffness of muscles or joints
- Stomach flu
- Yeast / fungus infection in mouth (oral thrush)
  - White patches usually on tongue or inner cheeks

The side effects that were likely a result of the lumbar puncture included:

- Back-pain
- Dizziness
- Feeling nauseous or throwing up
- Headache
- Pain during the injection
- Serious infections

Tell your doctor if you experience any of the side effects listed above. **Contact your doctor if you or your child has any side effect that bothers you or that does not go away.**

These are not all the possible side effects you may feel when taking SPINRAZA. If you experience any side effects not listed here, or have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, contact your healthcare professional.
**Reporting Side Effects**

You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.

**3 ways to report:**
- Online at [MedEffect](https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html);
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program  
    Health Canada, Postal Locator 1908C  
    Ottawa, ON  
    K1A 0K9  
    Postage paid labels and the Consumer Side Effect Reporting Form are available at [MedEffect](https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html).

*NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.*

**Storage:**

SPINRAZA will be managed and stored by healthcare professionals. Below are some of the guidelines for storing SPINRAZA:
- Refrigerate at 2°C to 8°C.
- May be stored at up to 30°C for up to 14 days.
- Protect from freezing.
- Protect SPINRAZA from light and keep it in the original carton until it is needed.
- Keep out of reach and sight of children.

**If you want more information about SPINRAZA:**
- Talk to your healthcare professional

This leaflet was prepared by Biogen Canada Inc.

Last Revised June 29, 2017