APPLICATION NUMBER:

209531Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)
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<tr>
<th>Application Type</th>
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<tr>
<td>Application Number</td>
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<td>Review Completion Date</td>
<td>December 13, 2016</td>
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<td>Subject</td>
<td>Evaluation of Need for a REMS</td>
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<td>Established Name</td>
<td>Nusinersen</td>
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<td>Trade Name</td>
<td>Spinraza™</td>
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<td>Name of Applicant</td>
<td>Biogen, Inc.</td>
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<td>Therapeutic Class</td>
<td>Antisense oligonucleotide</td>
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<td>Formulation(s)</td>
<td>12 mg in 5 mL solution</td>
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<td>Dosing Regimen</td>
<td>12 mg intrathecal administration. Loading doses on Days... (b)(4) followed by maintenance doses every 4 months.</td>
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<tr>
<td>Section</td>
<td>Page</td>
</tr>
<tr>
<td>--------------------------------------------------------------</td>
<td>------</td>
</tr>
<tr>
<td>EXECUTIVE SUMMARY</td>
<td>3</td>
</tr>
<tr>
<td>1 Introduction</td>
<td>3</td>
</tr>
<tr>
<td>2 Background</td>
<td>3</td>
</tr>
<tr>
<td>2.1 Product Information</td>
<td>3</td>
</tr>
<tr>
<td>2.2 Regulatory History</td>
<td>4</td>
</tr>
<tr>
<td>3 Therapeutic Context and Treatment Options</td>
<td>4</td>
</tr>
<tr>
<td>3.1 Description of the Medical Condition</td>
<td>4</td>
</tr>
<tr>
<td>3.2 Description of Current Treatment Options</td>
<td>5</td>
</tr>
<tr>
<td>4 Benefit Assessment</td>
<td>5</td>
</tr>
<tr>
<td>5 Risk Assessment &amp; Safe-Use Conditions</td>
<td>6</td>
</tr>
<tr>
<td>5.1 Serious Adverse Events</td>
<td>6</td>
</tr>
<tr>
<td>5.2 Post Lumbar Puncture Associated Adverse Events</td>
<td>7</td>
</tr>
<tr>
<td>5.3 Neurologic Toxicity</td>
<td>7</td>
</tr>
<tr>
<td>5.4 Laboratory Abnormalities</td>
<td>7</td>
</tr>
<tr>
<td>6 Expected Postmarket Use</td>
<td>8</td>
</tr>
<tr>
<td>7 Risk Management Activities Proposed by the Applicant</td>
<td>8</td>
</tr>
<tr>
<td>8 Discussion of Need for a REMS</td>
<td>8</td>
</tr>
<tr>
<td>9 Conclusion &amp; Recommendations</td>
<td>9</td>
</tr>
<tr>
<td>10 Materials Reviewed</td>
<td>9</td>
</tr>
<tr>
<td>11 Appendices</td>
<td>10</td>
</tr>
<tr>
<td>11.1 References</td>
<td>10</td>
</tr>
</tbody>
</table>

Reference ID: 4026954
EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Spinraza™ (nusinersen) is necessary to ensure the benefits of this product outweigh its risks. Biogen submitted a rolling New Drug Application (NDA 209531) on August 9 and September 23, 2016, for nusinersen with the proposed indication of treatment of spinal muscular atrophy. The risks associated with the use of nusinersen for which a REMS is being evaluated include post-lumbar puncture events and potential neurologic toxicity. The Applicant did not submit a REMS with this application but proposed risk management activities that include long-term data collection in ongoing open label studies as well as post-marketing surveillance to assess the potential for rare adverse reactions.

Spinal muscular atrophy is a rare, serious, debilitating, and life-threatening genetic disease of children with no treatment other than supportive care. Nusinersen showed significant clinical benefit and fulfills an unmet medical need. The primary risk associated with nusinersen is related to the intrathecal method of administration; potential neurologic toxicity is an additional risk. Therefore, DRISK and the Division of Neurologic Products (DNP) agree that a REMS is not needed to ensure the benefits of nusinersen outweigh its risks.

1 Introduction

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Spinraza™ (nusinersen) is necessary to ensure the benefits of this product outweigh its risks. Biogen submitted a rolling New Drug Application (NDA 209531) on August 9 and September 23, 2016, for nusinersen with the proposed indication of treatment of spinal muscular atrophy. This application is under review in the Division of Neurology Products. The Applicant did not submit a REMS with the application but proposed risk management activities that include long-term data collection in ongoing open label studies, as well as post-marketing surveillance to assess the potential for rare adverse reactions.

2 Background

2.1 Product Information

Spinraza™ (nusinersen), a new molecular entity, is an antisense oligonucleotide proposed for the treatment of spinal muscular atrophy, an autosomal recessive disease that involves the survival motor neuron gene. Antisense oligonucleotides are synthetic single-stranded nucleic acids that bind to RNA and modify gene expression. Nusinersen is designed to bind to and modulate splicing of the survival motor neuron 2 (SMN2) gene pre-mRNA, which intends to promote inclusion of exon 7 in SMN2 and increase the production of a functional SMN protein.

Nusinersen is supplied as a 12 mg/5 mL solution and administered by intrathecal injection using a 12 mg dose given on Days (a) followed by a maintenance dose every 4 months. The drug will

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(a) FDAAA factor (F): Whether the drug is a new molecular entity.

(b) FDAAA factor (D): The expected or actual duration of treatment with the drug.

Reference ID: 4026954
likely be administered in various settings that include hospital-affiliated outpatient clinics, interventional radiology departments, and the operating room, as anesthesia/sedation and fluoroscopy or ultrasound will be required for drug administration in some patients. Nusinersen received orphan product designation in April 2011 and was granted Fast Track designation in November 2011. Nusinersen is not currently approved in any other country.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for NDA 209531 relevant to this review:

- 04/18/2011: Orphan product designation granted for the treatment of spinal muscular atrophy
- 08/09/2016: NDA 209531, Rolling Submission Part 1 of 2, for the treatment of spinal muscular atrophy received
- 09/23/2016: NDA 209531, Rolling Submission Part 2 of 2, for the treatment of spinal muscular atrophy received
- 10/31/2016: A post mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that there is currently no need for a REMS.

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

Spinal muscular atrophy (SMA) is an autosomal recessive disease caused by deletions or mutations in the survival motor neuron 1 (SMN1) gene. The most common mutation is a deletion of exon 7. Humans have a paralogous SMN2 gene that differs from SMN1 by 11 nucleotides, including a single nucleotide difference that causes skipping of exon 7. The skipping of exon 7 results in only low levels of SMN2 protein, which are insufficient on a functional level. Modulation of splicing of the SMN2 pre-mRNA to include exon 7 intends to increase the production of a functional compensatory SMN protein.

The incidence of SMA ranges from 4 – 10 per 100,000 live births, and the U.S. prevalence is estimated to be around 25,000 patients.

SMA is characterized by degeneration of the anterior horn cells in the spinal cord and motor nuclei in the lower brainstem, resulting in muscular atrophy and weakness. Patients with SMA have symmetric proximal muscle weakness that is greater in the lower than upper limbs. The disease is also associated with a restrictive, progressive respiratory insufficiency that leads to respiratory failure. SMA is classified as type 1 through 4 depending upon the age of onset and disease course. SMA type 1, also known as infantile spinal muscular atrophy, is the most common (approximately 60% of patients) and severe type

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c Paralogous genes originate by duplication wherein one copy of the gene receives a mutation that gives rise to a new gene with a new function, though that function is often related to the role of the ancestral gene.

d FDAAA factor (A): The estimated size of the population likely to use the drug involved.
of SMA. It typically presents in the neonatal period and progresses rapidly. Infants with SMA-1 have a severe symmetric flaccid paralysis, are unable to sit unsupported, and usually die within the first two years of life from respiratory failure and infection.\(^6\) SMA-2 (intermediate form) and SMA-3 (mild form) have a later onset and a less severe course. SMA-2 presents between 3 and 15 months of age; patients can sit but cannot walk independently, and death from respiratory complications typically occurs after two years of age. SMA-3 is less severe and typically presents with signs of weakness at or after one year of age and progresses to a chronic course; patients are able to walk but with difficulty. Adult onset of SMA (type 4) usually presents in the second or third decade of life and is the mildest variant.

### 3.2 Description of Current Treatment Options

Current treatment for SMA is supportive and directed at providing nutrition and respiratory assistance as needed, and treating or preventing complications. Physical therapy may be helpful.

### 4 Benefit Assessment\(^{fg}\)

The pivotal clinical study (Study CS3B) supporting this application is a multicenter, randomized, double-blind, multiple-dose, sham-controlled study of intrathecal nusinersen in 121 subjects with infantile-onset SMA. The study examined 12 mg doses of nusinersen. In infants less than 24 months of age, the dose was adjusted for the estimated cerebrospinal fluid (CSF) volume at that age to deliver an equivalent dose volume. Subjects received loading doses of nusinersen by intrathecal injection on Days 1, 15, 29, and 64, and then received maintenance doses once every 4 months. The primary efficacy endpoint was a responder analysis for the development of motor milestones using the Hammersmith Infant Neurological Examination (HINE). A responder was defined as a subject who improved in more motor milestone categories than worsened. Survival and additional measures of motor function, such as the Children’s Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND), served as secondary endpoints. Survival analyses were performed on the intent-to-treat population.

Analysis of the interim efficacy population, which was comprised of 82 subjects, found a statistically significantly greater percentage of subjects achieved a HINE motor milestone response in the nusinersen group (40%; n=20 of 52) compared to the control group (0%; n=0 of 30) (p<0.0001). Of note, five subjects achieved independent sitting and one subject achieved standing (which SMA-1 patients typically never achieve) whereas no subjects in the control group achieved these milestones. Although not statistically significant, neuromuscular function as measured by the CHOP INTEND score also improved in the infants who received nusinersen. 65% of infants who received nusinersen had at least a 4-point improvement in CHOP INTEND score compared to 4% of infants in the control group. An analysis of overall survival found a lower percentage of subjects in the nusinersen group (15%) died compared with the control group (32%), though this was not statistically significant.

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\(^6\) FDAAA factor (B): The seriousness of the disease or condition that is to be treated with the drug.


\(^g\) Massie T.  Statistical Review for Spinraza (nusinersen), NDA 209531, November 30, 2016.
As a result of the positive interim analysis, the Applicant decided to terminate the study early on the grounds that continuing a controlled study was no longer ethical.\(^h\)

## 5 Risk Assessment & Safe-Use Conditions\(^i\)

The safety population is comprised of 173 nusinersen-treated subjects in controlled and uncontrolled studies. 83 and 54 subjects had at least one and two years of exposure, respectively.

### 5.1 Serious Adverse Events\(^jk\)

In the controlled pivotal study, 12 of 80 subjects (15%) in the nusinersen group and 13 of 41 subjects (32%) in the control group died. 17 of the 25 deaths were due to respiratory disorders (nusinersen 7; control 10) including respiratory failure and respiratory arrest. Two subjects in each group died of cardio-respiratory arrest. Two subjects in the nusinersen group died of nervous system disorders, including one due to hypoxic brain injury after cardiorespiratory arrest, and one due to hypoxic-ischemic encephalopathy after aspiration. One subject in the nusinersen group had an unclear cause of death, and one subject in the control group expired after the patient had initiated palliative care. The clinical safety reviewer stated that the deaths were related to complications of the underlying SMA disease (with the exception of the case with an unclear cause of death).

Serious adverse events (SAEs) were reported in 56 subjects (70%) in the nusinersen group and 33 subjects (80%) in the control group. The clinical safety reviewer stated most of the SAEs were manifestations of SMA. The most common SAEs were respiratory distress (nusinersen versus control: 24% versus 24%), respiratory failure (21% versus 34%), pneumonia (18% versus 10%), acute respiratory failure (14% versus 17%), atelectasis (14% versus 5%), pneumonia aspiration (8% versus 10%), rhinovirus infection (8% versus 5%), pneumonia viral (6% versus 2%), and cardio-respiratory arrest (6% versus 7%). The clinical safety reviewer considered that obstructive atelectasis related to infection and mucus plugging may have contributed to the increased frequency of serious atelectasis, and that use of sedation with nitrous oxide may have contributed to at least one of these cases. In addition, cases of cardio-respiratory arrest were assessed by the safety reviewer as likely related to advanced disease.

\(^{h}\) FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.


\(^{j}\) Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

\(^{k}\) FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.
5.2 Post Lumbar Puncture Associated Adverse Events

Post lumbar puncture adverse events reported in the safety population included back pain (17%), post lumbar puncture syndrome (12%), headache (12%), vomiting (9%), nausea (5%), and other symptoms. Most of these events were reported in subjects with later-onset SMA (it's noted that subjects with infantile-onset SMA as infants are not yet able to verbally communicate symptoms). Two of the 21 post lumbar puncture syndrome events were categorized as SAEs.

Information regarding failed lumbar punctures was not systematically collected across the clinical development program. However, adverse events related to failed lumbar puncture attempts in infants with presymptomatic SMA included spinal cord hematoma, epidural hemorrhage and spinal subarachnoid hemorrhage, extradural hematoma, and subdural hematoma. These events were managed with the standard of care, and all events resolved.

5.3 Neurologic Toxicity

In the controlled study, a higher percentage of nusinersen-treated subjects experienced events within the MedDRA SOC nervous system disorders compared with the control group (10% versus 5%). No single event contributed to the higher incidence; nine events with different preferred terms were reported in 8 nusinersen-treated subjects, including nystagmus (2 reports), muscle contractions involuntary, seizure, drooling, brain injury, clonus, hypoxic-ischemic encephalopathy, and somnolence. Two of these events were SAEs; one subject experienced seizure in the setting of a brain injury event that was categorized as serious. A second subject experienced an SAE of cardiac arrest after aspiration of a tube feeding and hypoxic-ischemic encephalopathy. The clinical safety reviewer was of the opinion that these SAEs were unlikely related to nusinersen.

Evidence of neurotoxicity was reported in nonclinical studies of nusinersen in juvenile cynomolgus monkeys. Some animals showed dose-dependent hippocampal vacuolization, with necrotic cells identified in some monkeys who received a nusinersen dose equivalent of 130 to 520 mg total first year doses in humans (the adult human total first year dose is 72 mg). No cell necrosis or vacuolization was observed in animals that received a nusinersen first year total dose equivalent of 39 mg.¹

5.4 Laboratory Abnormalities m

Six of 56 (11%) nusinersen-treated subjects had a platelet level below the lower limit of normal, compared to 0 of 28 control subjects in Study CS3B. No patient had a platelet count less than 50,000 cells/µL in that study.

Proteinuria occurred in 17 of 51 (33%) nusinersen subjects with infantile onset SMA, compared to 5/25 (20%) control subjects. Proteinuria occurred in 26 of 52 (69%) later-onset SMA subjects with a longer duration of treatment. Treatment-emergent low serum bicarbonate occurred in 32 of 48 (67%) of

¹ The 39 mg dose equivalent in monkeys is half the human first-year dose (72 mg) but similar to the yearly human chronic maintenance dose (36mg).
m Laboratory abnormalities were nonserious adverse events (except when stated otherwise) or were not coded as adverse events.
nusinersen subjects in whom it was measured; measurements from a control group were not performed.

In Study CS3B, 1 of 59 (2%) nusinersen subjects had treatment-emergent low serum sodium, compared to 0 of 28 control subjects. Of all treated nusinersen subjects, 6 of 151 (4%) had at least one low serum sodium measurement. Three subjects had hyponatremia below 130 mmol/L. One of these events was a severe and serious adverse event that the clinical safety reviewer considered possibly related to nusinersen. The patient required sodium supplementation during the time of subsequent nusinersen doses.

In Study CS3B, 2 of 55 (4%) nusinersen-treated subjects had an alanine aminotransferase (ALT) level greater than 3 times the upper limit of normal, compared to 0 of 25 control subjects. There were no cases of Hy's law drug-induced liver injury.

6 Expected Postmarket Use

Nusinersen is likely to be prescribed by pediatric neurologists, and perhaps by other members of the multidisciplinary clinical teams that manage SMA patients. The use of imaging or sedation will limit the practice setting for drug administration, and lumbar puncture is routinely performed for diagnostic and therapeutic purposes in children and infants and is generally a safe procedure. Therefore, it is expected that the drug will be administered by neurologists, radiologists, and pediatric anesthesiologists in various hospital settings that include interventional radiology departments, affiliated outpatient clinics, and the operating room.

7 Risk Management Activities Proposed by the Applicant

The Applicant did not submit a REMS with this application but proposed risk management activities that include long-term data collection in ongoing open label studies, as well as post-marketing surveillance to assess the potential for rare adverse reactions.

8 Discussion of Need for a REMS

Spinal muscular atrophy is a rare, serious, life-threatening genetic disease of children that is usually lethal in infants. There are no approved treatments for SMA at this time, and current clinical management is limited to supportive care. The pivotal trial's interim efficacy analysis found a substantially greater percentage of subjects achieved a HINE motor milestone response in the nusinersen group compared to the control group. Five subjects achieved independent sitting and one subject achieved standing, whereas no subjects in the control group achieved these milestones.

The potential serious adverse reactions of nusinersen include post lumbar puncture events, hyponatremia, and potential neurotoxicity. The clinical safety reviewer recommends describing several additional issues, including thrombocytopenia, renal effects, and hepatic effects as well as monitoring...
recommendations, in the warnings and precautions section of the label based on their being class effects observed with other oligonucleotide treatments.

Lumbar puncture can be technically difficult in SMA patients with scoliosis, spinal rods, or other hardware, however, the risks of lumbar puncture and the management of associated adverse events are well-known in the medical community. Ultrasound guidance was frequently used in the clinical studies, and is preferred to fluoroscopy to minimize repeated radiation exposure. The Applicant’s proposed prescribing information states that sedation should be considered as indicated by the clinical condition of the patient, and that ultrasound or other imaging techniques should also be considered to guide intrathecal administration of nusinersen, particularly in younger patients.

Neurotoxicity is another potential safety concern based primarily on animal data at this time, and the risk is likely to require a warning and precaution in the professional labeling. Pediatric neurologists who specialize in the treatment of SMA and perhaps other members of the multidisciplinary clinical teams that manage SMA patients are the likely prescribers of nusinersen. The use of imaging or sedation will limit the practice setting where nusinersen will be administered. At this time, this reviewer is not recommending a REMS for the management of the potential risks of nusinersen therapy.

9 Conclusion & Recommendations

Based on the available data a REMS is not necessary to ensure the benefits of nusinersen outweigh the risks. Spinal muscular atrophy is mainly treated in specialty centers by healthcare providers with detailed knowledge of the disease and the risks of treatment, who are familiar with the importance of patient monitoring.

Should DNP have any concerns or questions or if new safety information becomes available, please send a consult to DRISK.

10 Materials Reviewed

The following is a list of materials informing this review:


3. Biogen. Nonclinical Overview for nusinersen, September 23, 2016,


11 Appendices

11.1 REFERENCES

1 Bodamer OA. Spinal muscular atrophy. In:UpToDate, Nordli DR, Firth HV, Martin R (Eds), UpToDate, Waltham, MA 2016.
3 Rodichok L and Farkas R. Breakthrough Therapy Designation Review for ISIS 396443, IND 110011, August 22, 2014.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ROBERT G PRATT
12/13/2016

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12/13/2016