Summary of Risk Management Plan (RMP)

Spinraza® (Nusinersen)

Biogen Switzerland AG

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SUMMARY OF THE RISK MANAGEMENT PLAN (RMP) FOR SPINRAZA (NUSINERSEN)

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them.

The RMP summary of Spinraza is a concise document and does not claim to be exhaustive. As the RMP is an international document, the summary might differ from the "Arzneimittelinformation / Information sur le médicament" approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of Spinraza in Switzerland is the "Arzneimittelinformation/ Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. Biogen Switzerland AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of Spinraza.

Overview of disease epidemiology

Spinal muscular atrophy (SMA) is a genetic disease caused by a shortage of a particular protein (called survival of motor neuron, or SMN). This results in the loss of nerve cells in the spine, leading to weakness of the muscles in the shoulders, hips, thighs, and upper back. SMA may also weaken the muscles used for breathing and swallowing. SMA is considered an orphan disease, which means that it affects fewer than 200,000 people in each country. SMA occurs in between 8.5 to 10.3 per 100,000 live births.

Nusinersen works by helping the body to produce more of the SMN protein that people with SMA don't have enough of. This reduces the loss of nerve cells and so improves muscle strength.

Summary of treatment benefits

Spinraza is used to treat a genetic disease called SMA. Spinraza is one of a group of medicines known as antisense oligonucleotides (ASO). It contains the active substance nusinersen.

Spinraza works by helping the body to produce more of the SMN protein that people with SMA are short of. This reduces the loss of nerve cells and so improves muscle strength.

Unknowns relating to treatment benefits

It is unclear if there are additional unknown factors that might influence the response to nusinersen. It is uncertain what the appropriate amount of SMN protein is to remain symptom-free.

Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
None	Not applicable	Not applicable

Important potential risks

Risk	What is known (including reason why it is considered a potential risk)	Preventability
Thrombocytopenia and coagulation abnormalities	Coagulation abnormalities and thrombocytopenia, including acute severe thrombocytopenia, have been observed after administration of other subcutaneously or intravenously administered antisense oligonucleotides.	If clinically indicated, platelet and coagulation laboratory testing is recommended prior to administration of Spinraza.
Renal toxicity	Renal toxicity has been observed after administration of other subcutaneously and intravenously administered antisense oligonucleotides.	If clinically indicated, urine protein testing (preferably using a first morning urine specimen) is recommended. For persistent elevated urinary protein, further evaluation should be considered.
Hydrocephalus	There have been reports of communicating hydrocephalus not related to meningitis or bleeding in patients treated with nusinersen in the post-marketing setting. Some patients were implanted with a ventriculo-peritoneal shunt. In patients with decreased consciousness, an evaluation for hydrocephalus should be considered. d	Not known

Missing information

Risk	What is known
Safety profile in patients >18 years of age	Limited data in patients over the age of 18 years nusinersen has not been studied in the elderly population.
Safety profile in patients with severe and progressive scoliosis	Patients with severe scoliosis were not included in the clinical trials of Spinraza. Scoliosis has been observed in the Spinraza clinical studies, as these are expected events in patients with later-onset SMA, and patients did not discontinue in this setting. Scoliosis does not have an impact on the mechanism of action of nusinersen. Ultrasound (or other imaging techniques) may be considered to guide intrathecal administration of Spinraza, in patients with scoliosis..
Safety profile in patients receiving repetitive Lumbar Punctures (LP)	The data are limited in patients with longer drug exposure who have received repetitive LPs. In the Spinraza clinical studies, no adverse trend or pattern was identified with multiple LPs, and no patients have discontinued due to AEs related to LPs.
Safety profile in patients with long-term exposure to nusinersen	Spinraza is a treatment for life. The clinical trials performed were of a limited duration and the long-term safety of Spinraza is being monitored in on-going studies and in post marketing setting
Safety profile in pregnant or breastfeeding women	There are no data on the use of nusinersen in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity It is unknown whether nusinersen/metabolites are excreted in human milk. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Spinraza therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.
Safety profile in patients with low or higher *SMN2* copy number and/or different disease severity from the majority of patients in the nusinersen clinical programme (e.g., Type 0 and Type IV SMA)	The mechanism of action of nusinersen is the same across all patients, regardless of the number of *SMN2* gene copies, age at onset of disease, or disease severity. No data are available in Type 0 and Type IV SMA patients. If Type 0 or Type IV patients would receive nusinersen, their safety profile would be further assessed in the postmarketing setting.

Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) that provides physicians, pharmacists, and other health care professionals with details on how to use the medicine and the risks and recommendations for minimising them. An abbreviated version of this in lay language is also provided for use by patients in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

There are no additional risk minimisation measures.

Planned post authorisation development plan

Study/activity (including study number)	Objectives	Safety concerns /Efficacy issue addressed	Status	Planned date for submission of final results
Study SM202 (EMBRACE)	This is a Phase 2, randomized, double-blind, sham- procedure controlled study to assess the safety, tolerability, PK, and efficacy in patients who were not eligible to participate in studies CS3B or CS4. In light of emergent data, Part 1 of the study was terminated early and all subjects were rolled over into the open-label Part 2 of the study.	Long-term safety, tolerability, PK and efficacy data for patients with infantile and later onset SMA assessed for up to ~43 months. Cardiac safety.	Ongoing	2019
MDA US Neuromuscular Disease Registry	Prospective longitudinal registry in a research agreement with the Muscular Dystrophy Association. As of January 2017, 28 participating clinics across the US, with 205 unique patients diagnosed across the spectrum of SMA. Data collection generally include patient demographics, SMN copy numbers, motor milestones, vital status, surgical history, hospitalisations, medications, mobility, scoliosis, other comorbidities, nutritional therapies, pulmonary function and devices, and cause of death.	Missing information: safety profile in patients with low or higher *SMN2* copy number and/or different disease severity from the majority of patients in the nusinersen clinical programme (e.g., Type 0 and Type IV SMA); safety profile of patients >18 years	Ongoing	Synopsis of available data and data fields in the MDA dataset: Within 1 month after EC decision
International SMA Consortium (ISMAC) natural history study	Longitudinal natural history study with the 3 regional centres that comprise the ISMAC (SMA Reach UK, Italian SMA Network, and Dr. Richard Finkel at Nemours Children's Health System). Outputs expected to include baseline characteristics of treated patients and longitudinal data on nusinersen treatment patterns, motor function, respiratory function, hospitalisations, and comorbidities.	Missing information: safety profile in patients with low or higher *SMN2* copy number and/or different disease severity from the majority of patients in the nusinersen clinical programme (e.g., Type 0 and Type IV SMA); safety profile of patients >18 years	Ongoing	Updates to be provided in PSURs
TREAT-NMD Alliance registries	Longitudinal natural history studies in a research agreement with the TREAT-NMD Alliance to expand current registries to include nusinersen treatment information. The Global SMA Patient Registry consists of 26 national patient registries representing 29 countries (20 countries in Europe), collecting data from genetically confirmed patients across the spectrum of SMA. Data are self-reported and/or provided by healthcare professionals. More than 5000 SMA patients worldwide	Missing information: safety profile in patients with low or higher *SMN2* copy number and/or different disease severity from the majority of patients in the nusinersen clinical programme (e.g., Type 0 and Type IV SMA); safety profile of patients >18 years	Ongoing	Updates to be provided in PSURs

Study/activity (including study number)	Objectives	Safety concerns /Efficacy issue addressed	Status	Planned date for submission of final results
	have been enrolled in TREAT-NMD-associated registries.			
Study CS11 (SHINE) An Open-Label Extension Study for Patients With Spinal Muscular Atrophy Who Previously Participated in Investigational Studies of ISIS 396443	This is an open-label extension study in subjects with SMA who previously participated in investigational studies of ISIS 396443. The primary purpose of this study is to gather additional information on the long-term safety, tolerability, and efficacy of repeated doses of nusinersen (12 mg) administered as IT injections by lumbar puncture (LP) over an additional period of 5 years (totalling up to 8+ years with time in index study).	Long-term safety and efficacy	Ongoing	Q2 2024
Study CS5 (SM201/NURTURE) An Open-Label Study to assess the efficacy, safety, tolerability, and pharmacokinetics of multiple doses of ISIS 396443 delivered intrathecally to subjects with genetically diagnosed and presymptomatic Spinal Muscular Atrophy	This is a Phase 2, open-label study to assess the efficacy, safety, tolerability, and PK of multiple doses of ISIS 396443 in subjects with genetically diagnosed and presymptomatic SMA.	Long-term safety and efficacy	Ongoing	April 2023

Studies which are a condition of the marketing authorisation

Studies CS11 (SHINE) and CS5 (NURTURE / SM201) are conditions of the marketing authorization

Summary of changes to the Risk Management Plan over time

Not applicable.