



Seirbhís Sláinte
Níos Fearr
á Forbairt

Building a
Better Health
Service

NUSINERSEN (Spinraza®) PROTOCOL FOR THE TREATMENT OF SPINAL MUSCULAR ATROPHY (SMA)

Nusinersen (Spinraza[®]) for the treatment of Spinal Muscular Atrophy

Brand Name: Spinraza[®] 12 mg solution for injection.

Formulation and Composition: Vial containing solution for injection. Each 5 ml vial contains nusinersen sodium equivalent to 12 mg nusinersen.

Route of Administration: Intrathecal injection by lumbar puncture.

Dose: A loading dose of 12mg (5ml), by intrathecal injection, on days 0, 14, 28 and 63; followed by a maintenance dose of 12mg (5ml) once every 4 months thereafter.

Duration of treatment: Information on long term efficacy of this medicinal product is not available. The need for continuation of therapy should be reviewed regularly and considered on an individual basis depending on the patient's clinical presentation and response to the therapy. See *Stopping Criteria* section below.

Ex-Manufacturer Price: €83,300 (ex-VAT).

Alternative Price in Place: Yes, Commercial in Confidence discount in place. Please contact the company (Biogen) for pricing information.

Licensed Indication: Nusinersen (Spinraza[®]) is indicated for the treatment of 5q Spinal Muscular Atrophy (SMA).

HSE Reimbursed Indications: The HSE has approved the use of nusinersen (Spinraza[®]) for children aged under 18 years with genetically confirmed Spinal Muscular Atrophy (SMA) Types I, II or III. Approval is subject to the commercial terms discussed / offered by the company (Biogen).

Patients are prioritised on the basis of clinical need and the potential for treatment benefit.

Approval Process:

The following outlines the process for individual treatment approvals:

1. An individual application is submitted by the prescribing clinician to the HSE-Medicines Management Programme (MMP).
2. The HSE-MMP review the application with two possible outcomes:
 - a. HSE-MMP make a positive recommendation for treatment
 - b. HSE-MMP do not recommend treatment
3. HSE-MMP notifies the Assistant National Director for Acute Operations of their recommendation.
4. The Assistant National Director for Acute Operations notifies the prescribing consultant and the Hospital Group CEO of the final decision.

Protocol: SMA - Nusinersen	Published: November 2019 Review: November 2021	Version number: 1.0
NDMP Protocol Code: SMA001	Contributor: Dr. Declan O'Rourke MD FRCPI DCH, Consultant Paediatric Neurologist, Children's Health Ireland at Temple Street, Dublin 1	Page 2 of 7
Any clinician seeking to apply or consult these documents is expected to use independent medical judgement in the context of individual clinical circumstances to determine any patient's care or treatment. Use of these documents is the responsibility of the prescribing clinician and is subject to HSE's terms of use available at http://www.hse.ie/eng/Disclaimer <i>This information is valid only on the day of printing, for any updates please check https://www.hse.ie/eng/about/who/acute-hospitals-division/drugs-management-programme/protocols/</i>		

Inclusion criteria:

- Genetically confirmed Spinal Muscular Atrophy (SMA) Types I, II or III.
- Children aged under 18 years.
- Treatment is provided by the company at the agreed Commercial in Confidence price.

Exclusion criteria:

- Any contraindication to treatment as set out in the Summary of Product Characteristics for nusinersen (Spinraza®).
- Nusinersen will not be offered to patients with other life limiting conditions.
- SMA specific: SMA Type 0 is a special category by virtue of its extreme severity, and which requires discussion with the parents on the basis that SMA Type 0 infants are very unlikely to respond to nusinersen. Thus nusinersen is not an appropriate intervention for SMA Type 0 infants.
- Clinical and genetic diagnosis of SMA is not fulfilled.
- Current participation in a clinical trial with an investigational gene therapy for SMA
- Comorbidities that might preclude lumbar puncture, including but not limited to:
 - o Untreated bleeding disorders or any other existing condition which precludes lumbar punctures
 - o Hypoxaemia (oxygen saturation awake <96% or oxygen saturation asleep <96%, without ventilation support) during lumbar puncture evaluation.
 - o Presence of an untreated or inadequately treated active infection requiring systemic antimicrobial therapy (including antiviral or antifungal therapy).
 - o History of brain or spinal cord disease that would interfere with the lumbar puncture procedures, cerebrospinal fluid (CSF) circulation, or safety assessments.

Stopping Criteria:

i. Stopping Criteria for Early-Onset SMA Type I (Non-Sitters)

Frequency of assessments: Formally assess just prior to dose 7 and every 4 months thereafter.

- **CHOP-INTEND (Children’s Hospital of Philadelphia Infant Test of Neuromuscular Disorders) score:** Discontinue if there is no improvement of greater than 4 points from baseline, assessed just prior to dose 7. Reassess after every dose. Discontinue if there is a reduction in CHOP-INTEND scores of >4 points corroborated by two consecutive measurements* thereafter.
- **HINE-2 (Hammersmith Infant Neurological Examination) score:** Discontinue if there is no improvement greater than 2 points in ability to horizontal kick (or maximal score), or greater than or equal to 1-point improvement in any other milestone, excluding voluntary grasp, just prior to Dose 7. Discontinue if there is a reduction in HINE-2 scores (>2 points in ability to horizontal kick, or 1-point on any other milestone, excluding voluntary grasp) corroborated by two consecutive measurements* thereafter.

Protocol: SMA - Nusinersen	Published: November 2019 Review: November 2021	Version number: 1.0
NDMP Protocol Code: SMA001	Contributor: Dr. Declan O'Rourke MD FRCPI DCH, Consultant Paediatric Neurologist, Children's Health Ireland at Temple Street, Dublin 1	Page 3 of 7

Any clinician seeking to apply or consult these documents is expected to use independent medical judgement in the context of individual clinical circumstances to determine any patient's care or treatment. Use of these documents is the responsibility of the prescribing clinician and is subject to HSE's terms of use available at <http://www.hse.ie/eng/Disclaimer>

This information is valid only on the day of printing, for any updates please check <https://www.hse.ie/eng/about/who/acute-hospitals-division/drugs-management-programme/protocols/>

- Respiratory function: Discontinue if, after Dose 6 onwards, ventilation assistance is required for more than 16 hours per day for 21 consecutive days in the absence of simultaneous respiratory infection.
- Other Stopping Criteria:
- If in parents' view the quality of life is poor because of SMA Type I disability progression, or adverse effects of nusinersen administration procedure or drug side-effects, then discuss discontinuation.
- If in the treating physician view the handling and positioning required for lumbar puncture or sedation or a general anaesthetic required for this procedure, impose significant life-threatening risk then, this would be considered as an indication to stop nusinersen.
- If in the physicians view the patient is not adhering to internationally agreed Standard of Care guidelines for Spinal Muscular Atrophy.
- There may be additional unforeseen circumstances which may necessitate a discussion with the parents to discontinue treatment.

** In order to allow for confirmation of worsening and not an 'off' assessment day.*

ii. **Stopping Criteria for Late-Onset SMA Type II (Sitters)**

Frequency of assessments: Formally assess just prior to Dose 7 and every 4 months thereafter.

- HSFME (Hammersmith Functional Motor Scale Expanded) score: Discontinue if there is no improvement of > 3 points from baseline as measured just prior to dose 7. Discontinue if >3 points loss, corroborated by 2 consecutive measurements* after Dose 6.
- RULM (Revised Upper Limb Module) score: Discontinue if there is no improvement from baseline as measured just prior to dose 7. Discontinue if worsening, corroborated by 2 consecutive measurements* after Dose 6.
- Respiratory function: Discontinue if, after Dose 6 onwards, ventilation assistance is required for more than 16 hours per day for 21 consecutive days in the absence of simultaneous respiratory infection.
- Other Stopping Criteria:
 - If in parents' view the quality of life is poor because of SMA disability progression, or adverse effects of nusinersen administration procedure or drug, side effects, then discuss discontinuation.

Protocol: SMA - Nusinersen	Published: November 2019 Review: November 2021	Version number: 1.0
NDMP Protocol Code: SMA001	Contributor: Dr. Declan O'Rourke MD FRCPI DCH, Consultant Paediatric Neurologist, Children's Health Ireland at Temple Street, Dublin 1	Page 4 of 7
<p>Any clinician seeking to apply or consult these documents is expected to use independent medical judgement in the context of individual clinical circumstances to determine any patient's care or treatment. Use of these documents is the responsibility of the prescribing clinician and is subject to HSE's terms of use available at http://www.hse.ie/eng/Disclaimer</p> <p><i>This information is valid only on the day of printing, for any updates please check https://www.hse.ie/eng/about/who/acute-hospitals-division/drugs-management-programme/protocols/</i></p>		

- If the view of the treating physician is that the handling and positioning required for lumbar puncture or a general anaesthetic required for this procedure, impose significant life-threatening risk in a fragile SMA child/adult, this would be considered as an indication to stop nusinersen.
- If in the physicians view the patient is not adhering to internationally agreed Standard of Care guidelines for Spinal Muscular Atrophy.
- There may be additional unforeseen circumstances which may necessitate a discussion with the parents to discontinue treatment.

** In order to allow for confirmation of worsening and not an 'off' assessment day.*

iii. **Stopping Criteria for Late onset SMA Type III (Ambulatory)**

Frequency of assessments: Formally assess just prior to dose 7 and every 4 months thereafter.

- **6MWT (Six Minute Walk Test):** Discontinue if no improvement from baseline as measured just prior to Dose 7. Discontinue if worsening, as corroborated by two consecutive measurements* after Dose 6.
- **HSFME (Hammersmith Functional Motor Scale Expanded) score:** Discontinue if there is no improvement of > 3 points from baseline as measured just prior to dose 7. Discontinue if >3 points loss, corroborated by 2 consecutive measurements* after Dose 6.
- **Other Stopping Criteria:**
 - If in parents' view the quality of life is poor because of SMA disability progression, or adverse effects of nusinersen administration procedure or drug, side effects, then discuss discontinuation.
 - If the view of the treating physician is that the handling and positioning required for lumbar puncture or a general anaesthetic required for this procedure, impose significant life-threatening risk in a fragile SMA child/adult, this would be considered as an indication to stop nusinersen.
 - If in the physicians view the patient is not adhering to internationally agreed Standard of Care guidelines for Spinal Muscular Atrophy.
 - There may be additional unforeseen circumstances which may necessitate a discussion with the parents to discontinue treatment.

** In order to allow for confirmation of worsening and not an 'off' assessment day.*

Protocol: SMA - Nusinersen	Published: November 2019 Review: November 2021	Version number: 1.0
NDMP Protocol Code: SMA001	Contributor: Dr. Declan O'Rourke MD FRCPI DCH, Consultant Paediatric Neurologist, Children's Health Ireland at Temple Street, Dublin 1	Page 5 of 7

Any clinician seeking to apply or consult these documents is expected to use independent medical judgement in the context of individual clinical circumstances to determine any patient's care or treatment. Use of these documents is the responsibility of the prescribing clinician and is subject to HSE's terms of use available at <http://www.hse.ie/eng/Disclaimer>

This information is valid only on the day of printing, for any updates please check <https://www.hse.ie/eng/about/who/acute-hospitals-division/drugs-management-programme/protocols/>

Administration:

- Nusinersen should only be administered in specialist centres with access to a Paediatric Neurologist or an Adult Neurologist with experience in managing infants with SMA Types I, II and III. There must also be access to a Respiratory Physician, Physiotherapist, and Care Coordinator experienced in managing infants with SMA Types I, II and III.
- The standard-of-care consensus guidelines for patients with SMA must be adopted in specialist centres providing nusinersen therapy (Neuromuscul Disord. 2017 Diagnosis and management of spinal muscular atrophy: Part 1&2).
- Staff involved in the administration of nusinersen therapy must be suitably qualified and trained to administer intrathecal injections to infants who may require sedation or anaesthesia.
- The appropriate protocols to administer intrathecal injections to infants who may require sedation or anaesthesia must be in place.
- Sedation may be required to administer nusinersen, as indicated by the clinical condition of the patient. Ultrasound (or other imaging techniques) may be considered to guide intrathecal administration of nusinersen, particularly in younger patients and in patients with scoliosis.
- Aseptic technique should be used when preparing and administering nusinersen; see Summary of Product Characteristics for further information.
- The health care professional who will be administering nusinersen must be aware of the risks of intrathecal injection and anaesthesia sedation in infants and children with SMA, and use internal protocols for sedation or anaesthesia as appropriate.
- Nusinersen is administered as an intrathecal bolus injection over 1 to 3 minutes, using a lumbar puncture needle. The injection must not be administered in areas of the skin where there are signs of infection or inflammation. It is recommended that the volume of cerebral spinal fluid (CSF), equivalent to the volume of nusinersen (5mls) to be injected, is removed prior to administration.

Additional Information

The information listed is not exhaustive; please refer to the Summary of Product Characteristics for full details on prescribing information. Available online from: <https://www.medicines.ie/medicines/spinraza-12-mg-solution-for-injection-33811/>

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

Protocol: SMA - Nusinersen	Published: November 2019 Review: November 2021	Version number: 1.0
NDMP Protocol Code: SMA001	Contributor: Dr. Declan O'Rourke MD FRCPI DCH, Consultant Paediatric Neurologist, Children's Health Ireland at Temple Street, Dublin 1	Page 6 of 7
<p>Any clinician seeking to apply or consult these documents is expected to use independent medical judgement in the context of individual clinical circumstances to determine any patient's care or treatment. Use of these documents is the responsibility of the prescribing clinician and is subject to HSE's terms of use available at http://www.hse.ie/eng/Disclaimer</p> <p><i>This information is valid only on the day of printing, for any updates please check https://www.hse.ie/eng/about/who/acute-hospitals-division/drugs-management-programme/protocols/</i></p>		

a maintenance dose is delayed or missed, nusinersen should be administered as soon as possible and dosing continued every 4 months.

- Special warnings and precautions for use:

- *Lumbar puncture procedure:* There is a risk of adverse reactions occurring as part of the lumbar puncture procedure (e.g. headache, back pain, vomiting). Potential difficulties with this route of administration may be seen in very young patients and those with scoliosis. The use of ultrasound or other imaging techniques to assist with intrathecal administration of nusinersen, can be considered at the physician's discretion.
- *Thrombocytopenia and coagulation abnormalities:* Thrombocytopenia and coagulation abnormalities, 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 nusinersen.
- *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. The benefits-and risks of nusinersen treatment in patients with a ventriculoperitoneal shunt are unknown at present and the maintenance of treatment needs to be carefully considered.

Protocol: SMA - Nusinersen	Published: November 2019 Review: November 2021	Version number: 1.0
NDMP Protocol Code: SMA001	Contributor: Dr. Declan O'Rourke MD FRCP DCH, Consultant Paediatric Neurologist, Children's Health Ireland at Temple Street, Dublin 1	Page 7 of 7
<p>Any clinician seeking to apply or consult these documents is expected to use independent medical judgement in the context of individual clinical circumstances to determine any patient's care or treatment. Use of these documents is the responsibility of the prescribing clinician and is subject to HSE's terms of use available at http://www.hse.ie/eng/Disclaimer</p> <p>This information is valid only on the day of printing, for any updates please check https://www.hse.ie/eng/about/who/acute-hospitals-division/drugs-management-programme/protocols/</p>		