Medicines Management Programme

Managed Access Protocol – Nusinersen

(Spinraza®) for the treatment of 5q Spinal Muscular Atrophy

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List of Abbreviations

ASO	Antisense oligonucleotide
CHOP-INTEND	Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders
CSF	Cerebral spinal fluid
HINE	Hammersmith Infant Neurological Examination
HSE	Health Service Executive
IT	Intrathecal
MAP	Managed Access Protocol
MMP	Medicines Management Programme
mRNA	messenger ribonucleic acid
NIV	Non-invasive ventilator
RHS	Revised Hammersmith Scale
RULM	Revised Upper Limb Module
SMA	Spinal Muscular Atrophy
SMN	Survival motor neurone
SmPC	Summary of product characteristics

1. Nusinersen

Nusinersen is an antisense oligonucleotide (ASO) which modifies pre-messenger ribonucleic acid (mRNA) splicing of survival motor neuron 2 (SMN2) to promote increased production of full length SMN protein.

From July 2019, one presentation of nusinersen is available for reimbursement under hospital pricing approval as:

- Spinraza® 12 mg/5 mL solution for injection [i]

1.1 Licensed indication

Nusinersen is indicated for the treatment of 5q Spinal Muscular Atrophy (SMA).[i] The marketing authorisation includes all patients with SMA[ii], however this managed access protocol (MAP) relates specifically to SMA types I, II and III. SMA types 0 and type IV have not been approved for reimbursement by the Health Service Executive (HSE) and are not included in this MAP.

1.2 Reimbursement

Conditional reimbursement of Spinraza® under hospital pricing approval under this protocol is confined to the following subgroup of the licensed population:

- Patients with a clinical diagnosis of SMA Type 1, Type 2 or Type 3 who are aged < 18 years.

1.3 Licensed dose

Nusinersen is supplied in a 5 mL vial. Each 5 mL vial contains nusinersen sodium equivalent to 12 mg nusinersen. Each ml contains 2.4 mg of nusinersen.

Spinraza® is intended for intrathecal (IT) use by lumbar puncture. Table 1 details the recommended dosing for patients with 5q SMA. Please refer to the Summary of Product Characteristics (SmPC) for more information on posology and method of administration.

[i] Please refer to the summary of product characteristics for Spinraza® for full prescribing information.

[ii] Where the SMN1 gene becomes non-functional and is unable to produce the SMN protein, this is known as 5q-SMA. Mutations in other genes can also cause SMA; such cases of SMA are known as 'non-5q SMA'. Due to the rarity of 'non-5q SMA', 5q-SMA will be referred to as SMA throughout this document.

Table 1: Licensed dosing of nusinersen (Spinraza®) for the treatment of 5q SMA

Patient population	Route of administration	Dose
Infants and children under the age of 18 years	IT	**Loading dose** of 12 mg (5 mL) on days 0, 14, 28 and 63; followed by a **Maintenance dose** of 12 mg (5 mL) once every four months thereafter.

IT: intrathecal, mg: milligram, mL: millilitre

1.4 Application Process

Approved prescribers are required to apply for reimbursement approval on an individual patient basis. The *Application form for Medicines for the Treatment of Spinal Muscular Atrophy (SMA)* should be completed and sent by secure email to the Medicines Management Programme (MMP) at mmp@hse.ie.

See section 2 for further details on Reimbursement Criteria- Initiation

1.4.1 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 and notifies applicant of same.
3. HSE-MMP notifies the Office of the Assistant National Director for Acute Operations of their recommendation.
4. The Office of the Assistant National Director for Acute Operations notifies the prescribing consultant, the Hospital Group CEO and the HSE-MMP of the final decision.

If a patient is recommended for reimbursement of nusinersen, reimbursement will be supported for four vials of nusinersen (12mg/5mL) between days 1 and 63 and a maximum of one vial of nusinersen (a total of one Spinraza® 12mg /5mL vial) every four months thereafter i.e. in line with the licensed dose as per SmPC.

1.5 Reimbursement price

The price to wholesaler of the presentation of nusinersen available for reimbursement under hospital pricing approval as of March 2023, is as follows:

Table 2: Price to wholesaler of the presentation of nusinersen available under hospital pricing approval

Strength (pack size)	Price to wholesaler
Spinraza® 12 mg/5mL (1x 5mL vial)	€74,207.03*

mL: Millilitre, mg: Milligram; * price is correct as of March 2023

A commercial in confidence arrangement is in place with the marketing authorisation holder to reduce the net acquisition cost of Spinraza® to the HSE.

2. Reimbursement criteria - Initiation

This section outlines the criteria that must be satisfied in order for a patient to be recommended for reimbursement of nusinersen for the treatment of 5q-SMA under hospital pricing approval.

2.1 Prescribers

The prescribing of nusinersen under hospital pricing approval is confined to consultant neurologists with experience in the diagnosis and management of SMA in specialist centre(s) in Ireland, who have agreed to the terms of this MAP and have been approved by the HSE.

Applications for reimbursement approval will only be considered from these prescribers.

2.2 Diagnosis

For a positive reimbursement recommendation, clinicians will be required to confirm a diagnosis of 5q SMA type I, type II or type III at the time of application.

2.2.1 Genetic testing

Confirmed genetic diagnosis of 5q SMA is a condition of reimbursement. A copy of the genetic test should be included with the application for reimbursement approval.

2.2.2 Patient age

Applications for reimbursement approval will only be considered for individuals aged < 18 years at time of application.

2.3 Patient's medical treatment

Clinicians will be required to provide details of the patient's medical treatment at the time of application including any previous therapies used in the treatment of SMA. Reimbursement of Spinraza® will be conditional on its use as monotherapy in the treatment of SMA.

2.4 Patient's physical presentation

Clinicians will be required to provide details of the patient's physical presentation at the time of application e.g. limb function, speech, ability to sit unaided, roll, body strength, any supplementary requirements/supports.

2.5 Assessment scales

Clinicians will be required to provide details of the proposed assessment scale(s). The appropriate scale(s) is/are determined at baseline prior to the initiation of therapy and is/are based on the patient's motor ability. Appropriate scales include the following:

- Hammersmith Infant Neurological Examination (HINE)
- Revised Hammersmith Scale (RHS)
- Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND)

Assessment scales may additionally include:

- Revised Upper Limb Module (RULM)

2.6 Reimbursement exclusion criteria

In line with the exclusion criteria[iii] from the ENDEAR and CHERISH trials and *Technology appraisal guidance (TA588*), *NICE (2019), Variation agreement 16 January 2022,* reimbursement of nusinersen will not be considered in:

- Patients with any contraindication to treatment as set out in the SmPC for nusinersen (Spinraza®),
- Where the clinical and genetic diagnosis of SMA is not fulfilled,
- Patients with SMA Type 0 or type IV,
- Patients requiring permanent ventilation (≥16 hours/day for 21 consecutive days in the absence of acute reversible infection)/tracheostomy requirement at baseline,

[iii] This list is not exhaustive; please refer to the summary of product characteristics for Spinraza® for full prescribing information.

- Patients with additional life-limiting conditions where treatment with nusinersen would not provide long-term benefit,
- Patients who have comorbidities that might preclude lumbar puncture, including:
    - ✓ untreated bleeding disorder or any other exiting condition which precludes lumbar punctures,
    - ✓ hypoxaemia during lumbar puncture evaluation,
    - ✓ presence of untreated or inadequately treated active infection requiring systemic antimicrobial therapy (including antiviral or antifungal therapy),
    - ✓ history of brain or spinal cord disease that would interfere with the lumbar puncture procedures, cerebrospinal fluid circulation, or safety assessments.
- Patients who have had successful treatment with onasemnogene abeparvovec.
    - The definition of non-success is:

        a) **A reduction in motor ability:**

        Total worsening in scale score corroborated by two consecutive measurement from any two of the following three scales:

        - > 2 points on horizontal kick or 1 point on other HINE scores excluding voluntary grasp
        - > 4 points on the CHOP INTEND scale
        - > 3 points on the RHS scale

AND/OR

b) **A deterioration in respiratory function** defined as an increasing requirement for respiratory support overnight and/or, for that patient, an uncharacteristic increase in respiratory infections requiring hospital treatment that cannot be accounted for by aspiration or intrinsic lung disease.

3. Reimbursement criteria – Discontinuation

All patients should be formally assessed at baseline and at each subsequent maintenance dose of nusinersen (i.e. every four months) thereafter.

Stopping Criteria for all patients[iv]

a. Ventilation requirements

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.

b. Motor function

Frequency of assessments: Formally assess just prior to dose seven and every four months thereafter.

Where one scale has been measured from baseline, discontinue if total worsening in scale score corroborated by two consecutive measurements (in order to allow for confirmation of worsening and not an 'off' assessment day) is as follows:

- > 2 points on horizontal kick or one point on other HINE scores (excluding voluntary grasp)
- > 4 points on the CHOP-INTEND scale
- > 3 points on the RHS

Where two (or more) scales have been measured from baseline discontinue if there is total worsening in scale score(s), in the absence of any stability or improvement in other scales, corroborated by two consecutive measurements (in order to allow for confirmation of worsening and not an 'off' assessment day). For example, if a patient deteriorates on one scale but maintains stability or demonstrates improvement on another scale that has been measured since baseline (e.g. RULM) AND in the opinion of the treating clinician the patient continues to receive clinical benefit from treatment with nusinersen then continuation of treatment may be considered.

c. Administration requirements

Treatment must be discontinued if there is an inability to administer nusinersen by the intrathecal route.

Other Stopping Criteria for SMA Type I, II and III:

- If, in the parents' view, the quality of life is poor because of SMA disability progression, or adverse effects of nusinersen administration procedure or drug side effects.
- 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 patient with SMA.

[iv] In line with *Nusinersen for treating spinal muscular atrophy Technology appraisal guidance (TA588*), NICE (2019), Variation agreement 16 January 2022.

- Any additional unforeseen circumstances which may necessitate a discussion with the parents to discontinue treatment.

Following approval of a patient for reimbursement of nusinersen under hospital pricing approval, the prescribing clinician will be required to submit follow-up information to the MMP, as requested. Follow-up data may be requested by the MMP for audit purposes and provision of same is a condition of ongoing reimbursement.

3.1 Follow-up data

Patients should be assessed at each maintenance dose (i.e. every four months) to determine the effects of nusinersen on disease progression. Outcome data, appropriate to the patient, should be submitted and sent by secure email to the MMP (mmp@hse.ie) annually when requested, outlining:

- CHOP-INTEND scores, and/or other relevant outcome measures,
- Current requirement for non-invasive ventilator (NIV) support,
- Current requirement for non-oral nutrition,
- Any changes to clinical history since initiation.

4. Reimbursement criteria- Medicines Management

Approved site(s) must ensure a local policy is in place to ensure appropriate medicines management, including protocols for administration of nusinersen.

5. Prescribing of nusinersen (Spinraza® 12 mg/5mL solution for injection)

Please refer to the SmPC for nusinersen (Spinraza®) for full prescribing information including monitoring and patient counselling requirements. Only approved prescriber(s) will have access to prescribe nusinersen.

The following confirmations are required when prescribing nusinersen:

- Confirmation that nusinersen (Spinraza®) is being prescribed for a MMP approved patient in accordance with the MAP established in line with the terms of reimbursement approval given by the HSE.
- Confirmation that the prescriber will assist the HSE/MMP in their conduct of audits* through provision of information as requested, to provide assurance that the product is being prescribed in line with HSE reimbursement approval and the MAP.

- Confirmation that the patient's representative/guardian is aware that the application for reimbursement approval is being made on behalf of the patient and that audits may occur during which their personal data will be reviewed.

* Follow-up data may be requested by the HSE/MMP for audit purposes and provision of same is a condition of ongoing reimbursement.