NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Nusinersen for treating Spinal Muscular Atrophy (SMA)

Managed Access Agreement treatment criteria review; non-ambulant type III SMA population

Outline of review objectives

Review objectives

To review new evidence demonstrating the comparable clinical effectiveness of nusinersen for treating non-ambulant type III SMA patients compared to the population described by the company as 'later-onset SMA' in the original appraisal (those who were able to sit independently but never had the ability to walk independently).

Subject to the outcome of the evidence review, consider whether the eligibility criteria of the Managed Access Agreement (MAA) should be amended to expand access to type III SMA patients who no longer have independent ambulation.

Background

Spinal muscular atrophy, or SMA, is a rare genetic disorder that causes muscle weakness and progressive loss of movement. It is most commonly caused by defects in the gene *SMN1*, which leads to degeneration of motor neurones in the spinal cord (this is termed '5q SMA'). The motor neurones most affected by this condition are those that allow walking, crawling, arm movement, head and neck movement, swallowing and breathing. SMA causes substantial disability and may lead to increased mortality and reduced life expectancy. The most severe forms of SMA typically cause death before age 2 years, although people with later-onset types of SMA usually live into adolescence or adulthood. SMA also has substantial effects on families and carers, including the impact of caring for the patient, the need for specialist equipment and ongoing emotional, financial and social impacts.

SMA is a heterogeneous condition, which is clinically classified and often grouped into four main types, based on the age of onset of symptoms and the impact of the resulting muscle weakness on the person's ability to sit, and walk. The types of SMA decrease in severity from type I, in which symptoms arise before age 6 months, to type IV (adult-onset). Babies with SMA type I have low muscle tone (hypotonia) and severe muscle weakness which affects movement, swallowing and breathing. In type II SMA, the onset of symptoms is between 7 and 18 months of age, and people with this condition are often severely disabled and unable to walk unaided. Type III SMA is a heterogeneous condition, with a varying degree of muscle weakness appearing between age 18 months and 18 years; people with type III SMA can walk or sit unaided at some point, but many lose mobility over time.

In July 2019 NICE recommended nusinersen as an option for treating 5q spinal muscular atrophy (SMA) only if:

- people have pre-symptomatic SMA, or SMA types I, II or III and
- the conditions in the MAA are followed.
    - Access to treatment is conditional on a 5-year MAA, with data collection to address the significant uncertainties about the clinical benefits of nusinersen.
    - The MAA includes the following eligibility criteria:

      "If gained independent ambulation prior to initiation of therapy must still be independently ambulant, with the exception paediatric patients who have lost independent ambulation in the previous 12 months" (defined as prior to 28th July 2019)

      "Independent ambulation is defined as per the WHO definition: patient takes at least five steps independently in upright position with the back straight. One leg moves forward while the other supports most of the body weight. There is no contact with a person or object"
    - Patients with type III SMA who had lost independent ambulation over 12 months prior to the MAA publication are not eligible to start treatment with nusinersen as part of the MAA.

The NICE health technology appraisal committee was unable to make a recommendation for all patients with type III SMA who had lost the ability to walk because this population was not included in the key clinical trial (CHERISH) used to inform the economic model for those with 'later-onset' SMA. CHERISH recruited 126 patients who developed SMA symptoms between 6 months and 12 years and who were able to sit independently but never had the ability to walk independently.

Exceptionally for a MAA, following a request from NHS England and NHS Improvement and Biogen arising out of commercial negotiations, an evidence review clause was included in the agreement as follows:

> MAA clause 4.2: *The MAA Oversight Committee will consider any significant new evidence made available by Biogen in relation to the non-ambulant Type III SMA patients that may impact the eligibility criteria of the MAA. This does not commit any stakeholder to making an amendment to the MAA unless justified.*

In line with this clause, NICE will facilitate the MAA Oversight Committee (MAOC) to undertake a review of new evidence concerning non-ambulant SMA type III patients, as outlined below and in Appendix A.

The technology

Nusinersen (Spinraza, Biogen) is a 2'-O-methoxyethyl antisense oligonucleotide which stimulates the survival motor neuron (SMN)-2 gene to increase SMN protein levels. It is administered by intrathecal injection.

Nusinersen has a marketing authorisation in the UK for treating 5q SMA. It has been studied in clinical trials compared with placebo (sham procedure) in infants and children with SMA.

Intervention(s)	Nusinersen
Population(s)	People with type III 5q spinal muscular atrophy no longer have independent ambulation
Comparators	• Best supportive care • Comparable clinical benefit to those who were able to sit independently but never had the ability to walk independently.
Outcomes	The outcome measures to be considered collectively include: • motor function (including, where applicable, age-appropriate motor milestones and evidence of retention of fine motor skills) • respiratory function • complications of spinal muscular atrophy (including, for example, scoliosis and muscle contractures) • need for non-invasive or invasive ventilation • stamina and fatigue • mortality • adverse effects of treatment • health-related quality of life (if available).

Clinical Analysis	An External Assessment Centre (EAC) will be appointed by NICE to assess the new evidence and address the following questions for presentation to the Managed Access Oversight Committee (MAOC) to support the decision making process: 1. Is the new evidence of sufficient quality for decision making concerning the existing eligibility criteria with respect to non-ambulant type III SMA patients? 2. Does the new evidence demonstrate a comparable clinical benefit for non-ambulant type III paediatric and adult patients, as with those patients who were able to sit independently but never had the ability to walk independently, compared to best standard of care for all of the following outcomes collectively: o motor function (including, where applicable, age-appropriate motor milestones and evidence of retention of fine motor skills) o respiratory function o complications of spinal muscular atrophy (including, for example, scoliosis and muscle contractures) o need for non-invasive or invasive ventilation o stamina and fatigue o mortality o adverse effects of treatment o health-related quality of life (if available) 3. Does the new evidence provide sufficient new information and demonstrate a comparable clinical benefit for non-ambulant paediatric and adult patients to support a recommendation to amend the MAA eligibility criteria to expand access to non-ambulant type III SMA patients?
Economic analysis	No economic analysis will be undertaken
Other considerations	In the event of a final decision to amend the MAA eligibility criteria to expand access to type III SMA patients who no longer have independent ambulation stakeholders will be asked (during the 7-day MAOC stakeholder engagement stage) to consider the impact of this change on the starting and stopping criteria in the MAA and their continued appropriateness.

Appendix A: Nusinersen Managed Access Agreement treatment criteria review process

No.		
1	**Outline of evidence review objectives**	Managed Access (MA) team prepares an outline of objectives for the External Assessment Centre (EAC), company and Managed Access Oversight Committee (MAOC) and set out the scope of the evidence review.
2	**Review initiation: notification of deadline for new evidence submission**	The company and MAOC members are given formal notice of the need to submit data within 28-days to initiate the evidence review process. All new evidence is shared with the company in the first instance.
3	**External evidence review**	The EAC assess the new evidence and deliver recommendations in line with the Outline of Objectives document
4	**Clarification questions and responses**	During the review, the EAC sends any clarification questions to the company. The company have 7 days to respond to clarification questions.
5	**Managed Access Oversight Committee (MAOC) review**	The MAOC reviews the recommendations from the external evidence review and indicates whether they support the recommendations of the EAC.
6	**Stakeholder engagement**	The Managed Access (MA) Team prepares a brief concerning the outcome of the MAOC review for circulation to the MAOC. The MAOC are invited to submit any comments or requests for clarifications during a 7-day consultation period. Points of clarification are reviewed by the MA Team and updated details are incorporated into the final briefing stage that follows. A further meeting with stakeholders will be held if required.
7	**Final briefing**	MA team produce a brief summarising the evidence submitted and a short statement concerning the outcome for the MAOC for information only, prior to publication.
8	**Final recommendation publication**	The evidence submitted and a short statement concerning the outcome (and an amended, executed MAA, if applicable) are published on the NICE website.

Membership of the Managed Access Oversight Committee

The Managed Access Oversight Committee (MAOC) is a group of key stakeholders (including the agreement signatories) convened by the NICE Managed Access (MA) team to monitor the progress of the MAA throughout the agreement term. The nusinersen MAOC membership is as follows:

Voting members

- A representative from NHS England (who will also provide updates on behalf of the clinical panel)
- Two paediatric clinical experts in the treatment of children with spinal muscular atrophy
- One clinical expert in the treatment of adults with spinal muscular atrophy
- One physiotherapist involved in the treatment of spinal muscular atrophy
- A representative from Spinal Muscular Atrophy UK (patient organisation)
- A representative from Treat SMA (patient organisation)
- A representative from MDUK (patient organisation).

Non-voting members

- NICE Managed Access Associate Director
- NICE Technical Advisor or Analyst
- NICE Senior Manager Evidence Generation and Oversight
- SMA-REACH Clinical/Academic representative
- SMA-REACH (Global) Trial Manager
- A representative from the adult SMA data network
- Two standing representatives from Biogen (company) and 1 substitute representative. **Note:** Biogen representatives will be present for the first part of the MAOC review meeting only (during presentation of the evidence). The MAOC will deliberate and make their decision in private.

Observers/advisors

- NICE Technology Appraisals Committee C Chair (MAOC review meeting chair)
- NICE Technology Appraisals Committee C member
- Representatives from the External Assessment Centre.