NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Appraisal

Nusinersen and risdiplam for treating spinal muscular atrophy (review of TA588 and TA755)

Draft scope

Draft remit/evaluation objective

To appraise the clinical and cost effectiveness of nusinersen and risdiplam within their marketing authorisations for treating spinal muscular atrophy.

Background

Spinal muscular atrophy (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 symptom severity varies substantially and is often grouped into SMA types based on the age of onset of symptoms and the best motor function the person obtained. The types of SMA decrease in severity from type 0, in which symptoms arise before birth and babies survive for only a few weeks, to type 4 (adult-onset) which is associated with mild motor impairment and a normal life span. Types 0 and 4 are rarely diagnosed. In people with type 1 SMA, symptoms arise before 6 months and babies are unable to sit independently; babies with type 1 SMA have low muscle tone (hypotonia) and severe muscle weakness which affects movement, swallowing and breathing. In people with type 2 SMA, the onset of symptoms occurs at between 7 and 18 months, and people with this condition are often severely disabled and unable to walk unaided. People with type 3 SMA experience varying degrees symptom severity with muscle weakness appearing between age 18 months and 18 years; most people with type 3 SMA can walk or sit unaided at some point, but many lose mobility over time[1].

SMA may also be diagnosed pre-symptomatically through genetic testing. The number of SMN2 gene copies, which encodes the SMN protein that can partially compensate for the loss of the SMN1 gene, is inversely related to the severity of SMA and can be used to predict the course of the disease[2]. Currently in England only a small number of people are identified pre-symptomatically.

SMA affects an estimated 1 in 10,000 births worldwide,[3] and the incidence varies between different types of SMA. It is estimated that about 70 people were born with SMA in the UK in 2021, and there are currently between 1,200 and 2,500 children and adults in the UK living with SMA.[3]

NICE highly specialised technology appraisal guidance 15 recommends onasemnogene abeparvovec as an option for treating 5q spinal muscular atrophy with a bi-allelic mutation in the SMN1 gene and a clinical diagnosis of type 1 SMA in babies, only if they are 6 months or younger, or they are aged 7 to 12 months, and their treatment is agreed by the national multidisciplinary team. NICE highly specialised technology appraisal guidance 24 partially updated the guidance to also recommend onasemnogene abeparvovec for treating pre-symptomatic 5q spinal muscular atrophy (SMA) with a biallelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene in babies aged 12 months and under.

Nusinersen and risdiplam are currently available through managed access agreements. NICE technology appraisal guidance 588 and 755 recommended these technologies within their respective marketing authorisations for people who have pre-symptomatic SMA, or SMA types 1, 2 or 3 only if the conditions of the managed access agreements are followed.

For most of the population included in this appraisal, there are currently no active treatments for SMA routinely commissioned, and the condition would otherwise be managed through multidisciplinary supportive care. Treatment usually follows guidelines from the International Standards of Care Committee for Spinal Muscular Atrophy[4,5]. Treatment typically differs according to 3 functional levels of the patients: non-sitter, sitter, and walker. Supportive care strategies aim to minimise the impact of disability, address complications and improve quality of life. These may involve respiratory, gastroenterology, and orthopaedic care, as well as nutritional support, physiotherapy, assistive technologies, occupational therapy and social care.

The technologies

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.

Risdiplam (Evrysdi, Roche Products) is a small-molecule survival motor neuron-2 (SMN2) gene splicing modifier which increases SMN protein levels in the central nervous system and throughout the body. It is administered orally.

Risdiplam has a marketing authorisation in the UK for the treatment of 5q SMA in patients 2 months of age and older, with a clinical diagnosis of SMA type 1, type 2 or type 3 or those with one to four SMN2 copies.

Interventions	• Nusinersen • Risdiplam
Population	People with 5q spinal muscular atrophy

Subgroups	If the evidence allows the following subgroups will be considered: • SMA type • Number of SMN2 gene copies • Functional status (non-sitter, sitter, walker) • People who have had prior active treatment for SMA
Comparators	• Established clinical management • The interventions will be compared to each other In addition, for children aged 12 months and under with a bi-allelic mutation in the SMN1 gene and present with a clinical diagnosis of type 1 SMA or pre-symptomatically with up to 3 copies of the SMN2 gene • Onasemnogene abeparvovec
Outcomes	The outcome measures to be considered include: • motor function (including, where applicable, both age-appropriate gross motor milestones and fine motor skills) • bulbar function (including, for example, swallowing and ability to communicate) • frequency and duration of hospitalisation • 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 (for patients and carers).

Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability of any managed access arrangement for the intervention will be taken into account.
Other considerations	Guidance will only be issued in accordance with the marketing authorisations. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisations granted by the regulator.
Related NICE recommendations	**Related technology appraisals:** Risdiplam for treating spinal muscular atrophy (2021) NICE technology appraisal guidance 755 Nusinersen for treating spinal muscular atrophy (2019) NICE technology appraisal guidance 588 **Related highly specialised technology appraisals:** Onasemnogene abeparvovec for treating presymptomatic spinal muscular atrophy (2023) NICE highly specialised technology guidance 24 Onasemnogene abeparvovec for treating spinal muscular atrophy (2023) NICE highly specialised technology guidance 15
Related National Policy	The NHS Long Term Plan (2019) NHS Long Term Plan NHS England Manual for prescribed specialised services (2023). Chapters Services 11, 48, 119 and 134. NHS manual for prescribed specialist services 2023/24 NHS England (2018) Clinical Commissioning Policy Statement: Nusinersen for genetically confirmed Spinal Muscular Atrophy (SMA) type 1 for eligible patients under the Expanded Access Programme (EAP). Department of Health and Social Care (2023). England Rare Diseases Action Plan 2023

	NHS England. National Programmes of Care and Clinical Reference Groups: E04. Paediatric Neurosciences NHS England. Care and Clinical Reference Groups: D03. Spinal Services NHS England (2013/14). NHS standard contract for neurosciences: specialised neurology (adult) NHS England (2013) 2013/14 NHS standard contract for paediatric neurosciences- neurodisability. Reference: E09/S/c Department of Health (2005) National service framework for long term conditions Department of Health and Social Care (2022) The NHS Outcomes Framework

Questions for consultation

What treatments would be considered to be established clinical practice in the NHS for treating people with spinal muscular atrophy if nusinersen and risdiplam were not currently available through a managed access agreement?

What are the reasons children otherwise eligible for onasemnogene abeparvovec instead have treatment with nusinersen or risdiplam?

Do you consider that the use of nusinersen or risdiplam can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculations? Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits.

Are the outcomes listed appropriate?

Are there any subgroups of people in whom these technologies are expected to be more clinically effective and cost effective or other groups that should be examined separately?

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which nusinersen or risdiplam are licensed;

- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;

- could have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the committee to identify and consider such impacts.

NICE intends to appraise this technology through its Multiple Technology Appraisal (MTA) process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on NICE's health technology evaluation processes is available at: https://www.nice.org.uk/process/pmg36/chapter/introduction-to-health-technology-evaluation).

References

1. SMA UK (2018) What is 5q Spinal Muscular Atrophy? Accessed July 2023.
2. MedlinePlus (2018) SMN2 gene. Accessed July 2023.
3. SMA UK (2017) Information about SMA. Accessed June 2023.
4. Mercuri E, Finkel RS, Muntoni F et al. (2018) Diagnosis and management of spinal muscular atrophy: Part 1: Recommendations for diagnosis, rehabilitation, orthopedic and nutritional care. Neuromuscular Disorders 28(2): 103– 115
5. Finkel RS, Mercuri E, Meyer OH et al. (2018) Diagnosis and management of spinal muscular atrophy: Part 2: Pulmonary and acute care; medications, supplements and immunizations; other organ systems; and ethics. Neuromuscular Disorders 28(3): 197–207