NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Appraisal

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

Final scope

Draft remit/evaluation objective

To appraise the clinical and cost effectiveness of nusinersen and risdiplam within their marketing authorisations for treating 5q 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 can be subdivided into subtypes alluding to the spectrum nature of the disease. Categorising people into types consistently at presentation is difficult due to the variable nature of the disease. Types 0 and 4 are rarely diagnosed and therefore there is little evidence for these types. 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 of 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] and 90% of children with SMA type 3A lose the ability to walk before adult life with many people with type 3B SMA experiencing progressive weakness.[2,3]

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 broadly predict the course of the disease[4]. However, at an individual level, accurate predictions cannot be made about the type or severity of SMA based on the SMN2 copy number alone.[5,6] Currently in England only a small number of

people are identified pre-symptomatically where a sibling has been diagnosed with SMA but this may rise if newborn screening for SMA is implemented.

SMA affects an estimated 1 to 2 people in 10,000 births worldwide[7] and it is estimated that about 70 people were born with SMA in the UK in 2021, 60% with type 1 SMA. There are currently an estimated 1,340 children and adults in the UK living with SMA.[8]

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 routinely commissioned for patients with type 2 and 3 SMA, 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], which are currently under review. 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 SMN2 gene to increase SMN protein levels. It is administered by intrathecal injection.

Nusinersen has a marketing authorisation in the UK for treating pre-symptomatic and symptomatic 5q SMA. It has been studied in clinical trials compared with placebo (sham procedure) in infants and children with SMA and real-world evidence studying the effectiveness and safety of nusinersen across all age-groups.

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. 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 people with one to four SMN2 copies. It has been studied in clinical trials

through single-arm studies in infants and compared with placebo in children and adults (aged 2-25 years of age) with SMA.

Interventions	• Nusinersen • Risdiplam Interventions are monotherapies in addition to existing clinical services and established clinical management.
Population	People with types 0, 1, 2, 3 or 4 5q SMA, or pre-symptomatic 5q SMA confirmed with genetic testing with 1 to 4 SMN2 copies
Subgroups	If the evidence allows the following subgroups will be considered: • Number of SMN2 gene copies in people with pre-symptomatic SMA • Functional status (non-sitter, sitter, walker) • People who have had prior active treatment for SMA
Comparators	• Established clinical management • Best supportive care • 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 5q 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

References

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