NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Health Technology Appraisal

Risdiplam for treating spinal muscular atrophy

Final scope

Remit/appraisal objective

To appraise the clinical and cost effectiveness of risdiplam within its marketing authorisation for treating spinal muscular atrophy.

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 without treatment, 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 often grouped into 5 main types, based on the age of onset of symptoms and how much motor function the person has. 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). Babies with SMA type 1 have low muscle tone (hypotonia) and severe muscle weakness which affects movement, swallowing and breathing. In type 2 SMA, the onset of symptoms is between age 7 and 18 months, and people with this condition are often severely disabled and unable to walk unaided. Type 3 SMA is a heterogeneous condition, with a varying degree of 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. Adults with type 4 SMA often have mild motor impairment symptoms, such as walking difficulties, but rarely experience difficulties in breathing or swallowing.[1] Type 4 SMA causes increased muscle weakness with age but does not affect life expectancy.[1]

SMA affects an estimated 1 in 6,000 to 1 in 10,000 births worldwide,[2] and the incidence varies between different types of SMA. It is estimated that about 100 people are born with SMA per year in the UK, and there are currently between 1,200 and 2,500 children and adults in the UK living with SMA.[2]

The condition is managed through multidisciplinary supportive care. Treatment usually follows guidelines from the International Standards of Care Committee for Spinal Muscular Atrophy. 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. At present, nusinersen (Spinraza) is the only active treatment available for treating

SMA. Nusinersen is administered by intrathecal injection and is currently recommended for pre-symptomatic SMA or SMA types 1, 2 or 3 if the conditions in the managed access agreement are followed. However, as nusinersen is available via a managed access agreement, its use is not considered to be embedded in NHS clinical practice because its availability to patients is contingent on further evidence generation and re-appraisal by NICE. Additionally, the significant uncertainties identified prevented NICE's committee from making a positive recommendation during its appraisal, so it cannot be considered to be routinely commissioned. Therefore, for the purposes of this health technology evaluation, nusinersen will not be considered as a comparator.

The technology

Risdiplam (brand name unknown, 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 does not currently have a marketing authorisation in the UK for treating SMA. It is being studied in 4 ongoing trials:

- A single-arm trial in babies (aged 1 to 7 months old) with type 1 SMA;
- A randomised placebo-controlled trial in children and adults (aged 2 to 25 years) with type 2 or 3 SMA;
- A single-arm trial in babies, children and adults (aged 6 months to 60 years) with previously treated SMA;
- A single-arm trial in babies (aged from birth to 6 weeks) with genetically diagnosed SMA who are not yet presenting symptoms (pre-symptomatic).

Intervention	Risdiplam
Population	People with spinal muscular atrophy
Comparator	Best supportive care

Outcomes	The outcome measures to be considered include: • motor function (including, where applicable, age-appropriate motor milestones such as sitting, standing and walking) • 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
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.
Other considerations	If the evidence allows, consideration will be given to subgroups based on severity of disease (including people with pre-symptomatic disease and considerations such as age of SMA onset, SMA type and genotype [including SMN2 copy number]). Guidance will only be issued in accordance with the marketing authorisation. 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 authorisation granted by the regulator.
Related NICE recommendations and NICE Pathways	Nusinersen for treating spinal muscular atrophy (2019). NICE Technology Appraisal 588. Subject to the terms of the Managed Access Agreement. Review date by July 2024 Onasemnogene abeparvovec for treating spinal muscular

	atrophy type 1 [ID1473]. Publication expected March 2021.
Related National Policy	The NHS Long Term Plan, 2019. NHS Long Term Plan NHS England (2018/2019) Manual for prescribed specialised services 2018/19 Services 11, 48, 119 and 134 Department of Health and Social Care, NHS Outcomes Framework 2016-2017: https://www.gov.uk/government/publications/nhs-outcomes-framework-2016-to-2017 NHS England (2018) NHS England Funding and Resource 2018/19: Supporting 'Next Steps for the NHS Five Year Forward View' NHS England. Care and Clinical Reference Groups: D03. Spinal Services NHS England. Care and Clinical Reference Groups: E04. Paediatric Neurosciences NHS England. Care and Clinical Reference Groups: D04. Neurosciences

References

1. Spinal Muscular Atrophy UK. Symptoms, Diagnosis & Effects of 5q Spinal Muscular Atrophy. Accessed December 2019.

2. Spinal Muscular Atrophy UK. Summary information about SMA. Accessed November 2019.

