NICE National Institute for Health and Care Excellence

NICE guidance

Risdiplam for treating spinal muscular atrophy

Technology appraisal guidance
Published: 16 December 2021
Last updated: 15 December 2023

www.nice.org.uk/guidance/ta755

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Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

1 Recommendations

1.1 Risdiplam is recommended as an option for treating 5q spinal muscular atrophy (SMA) in people of all ages with a clinical diagnosis of SMA types 1, 2 or 3 or with pre-symptomatic SMA and 1 to 4 SMN2 copies. It is recommended only if the conditions of the managed access agreement are followed.

Why the committee made these recommendations

SMA is a rare genetic condition and there is an unmet need for effective treatments that can slow disease progression.

Clinical evidence shows that risdiplam improves motor function in SMA types 1 to 3. There is some evidence suggesting that people with type 1 SMA who have risdiplam live for longer. There is also some evidence suggesting risdiplam may be effective for people with pre-symptomatic SMA. But there is no direct evidence comparing risdiplam with usual care for type 1 SMA. And although it's likely that risdiplam has long-term benefits, there is no long-term evidence, so this is uncertain.

The cost-effectiveness estimates are higher than what NICE usually considers an acceptable use of NHS resources. So risdiplam cannot be recommended for routine use in the NHS. But because of the unmet need for effective treatments for SMA, risdiplam is recommended through a managed access agreement while more data is collected to address the uncertainties in the evidence.

2 Information about risdiplam

Marketing authorisation indication

2.1 Risdiplam (Evrysdi, Roche) is indicated for 'the treatment of 5q spinal muscular atrophy (SMA) in patients with a clinical diagnosis of SMA Type 1, Type 2 or Type 3 or with one to four SMN2 copies'.

Before the December 2023 licence extension, risdiplam was indicated only for people 2 months and over.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for risdiplam.

Price

2.3 The list price is £7,900 per 60-mg (80-ml) vial. The company has a commercial arrangement. This makes risdiplam available to the NHS with a discount. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

3 Committee discussion

The appraisal committee considered evidence submitted by Roche, a review of this submission by the evidence review group (ERG) and responses from stakeholders. See the committee papers for full details of the evidence.

The appraisal committee was aware that several issues were resolved during the technical engagement stage, and agreed that the company's treatment-effect plateau (which assumes people who have had risdiplam will not reach additional motor milestones after 66 months of treatment for type 1 SMA and 26 months for SMA types 2 or 3) is acceptable and consistent with NICE's technology appraisal guidance on nusinersen for treating spinal muscular atrophy (from now, TA588; see key issues 3, 6 and 7 in the ERG critique of the company's technical engagement response, page 12).

It discussed the following issues (issues 1, 2, 4, 5 and 8 to 10), which were outstanding after the technical engagement stage.

Clinical need

Spinal muscular atrophy is a rare, progressive neuromuscular disorder

3.1 Spinal muscular atrophy (SMA) is a rare, progressive neuromuscular disease caused by a genetic mutation in the SMN1 gene on chromosome 5q. People with the condition have a range of symptoms, including muscle weakness, and have worsening physical disability, mobility loss and respiratory dysfunction. SMA can be grouped into 5 main types (0 to 4), based on the age of onset and the maximum motor function reached. SMA type 0, the most severe, affects babies before birth. The babies do not develop any motor skills and often survive for only a few weeks after birth. Babies with type 1 SMA are unable to sit or roll because of severe muscle weakness, which gets worse over time. The muscle weakness also affects swallowing and breathing, and typically results in death within 2 years if respiratory support is not used. In type 2 SMA, the onset of symptoms is between 7 months and 18 months. People with this condition can sit

independently at diagnosis. However, progressive loss of motor function means they have a reduced life expectancy compared with the general population. In type 3 SMA there are varying degrees of muscle weakness, which appear between 18 months and 18 years. People with this condition can have a normal lifespan and walk or sit unaided, but many lose mobility and other functions over time. Type 4 SMA is the least severe and affects adults, who may have milder motor impairment and live a normal lifespan. The clinical experts explained that type 0 and type 4 SMA are rarely diagnosed in clinical practice in the NHS in England. The patient experts explained that SMA is a progressive disorder, so all patients experience more severe symptoms over time. The committee concluded that SMA is a rare, progressive neuromuscular disorder that affects all aspects of daily life.

The current SMA classification system has limitations but has been used in the marketing authorisation and clinical evidence for risdiplam

3.2 The patient experts commented that the SMA classification system does not always reflect the full extent of the disease. The boundaries between the different SMA types are blurred and can be subjective. They also explained that the classification system was not originally intended to define populations who were eligible for treatment. One patient expert with a child with type 3 SMA described how progressive loss of motor function has affected all daily activities. They noted that being unable to access treatments such as nusinersen has a big effect on physical and mental health. The committee understood that risdiplam's marketing authorisation includes types 1 to 3 SMA as currently defined by the SMA classification system, and these definitions were also used in the clinical evidence (see section 3.5). The committee acknowledged the limitations of the current SMA classification system but concluded that it had been used in the marketing authorisation and clinical evidence for risdiplam.

SMA severely affects the quality of life of patients, carers and their families

3.3 The clinical and patient experts explained that most people with SMA need constant support. This can include full-time care and attention, needing physical effort (such as lifting and carrying) and causing loss of sleep for patients and carers, stress, and fear about loss of abilities. One patient expert with a child with type 2 SMA described how living with the condition can put considerable strain on relationships with other family members and friends. Siblings have a restricted social circle because of the fear of respiratory infections, and often act as young carers. As well as dealing with the physical and mental stress as the condition progresses, the financial burden also increases as more supportive equipment is needed. Another patient expert with type 2 SMA described the fear of losing fine motor skills and how being unable to work would affect the whole family. All these factors have a large effect on family members' health-related quality of life. The patient experts emphasised how caring for people with SMA affects the whole family and can cause physical, mental and financial issues. The committee concluded that SMA has a substantial effect on the quality of life of patients, caregivers and their families.

Comparator

Best supportive care is the most appropriate comparator for risdiplam

3.4 Nusinersen was the only disease-modifying treatment available for SMA at the start of this appraisal. The clinical and patient experts explained that many people with SMA have spinal fusion (that is, spinal surgery to treat scoliosis) so cannot have nusinersen because it is delivered by intrathecal injection and requires access to the lower spine. They commented that an oral treatment option would be welcome. It would also address several issues related to the delivery of nusinersen including the use of sedation, radiographic imaging and anxiety associated with lumbar puncture. Nusinersen is recommended in TA588 through a managed access agreement. This makes nusinersen available while more data is collected. However, nusinersen is not routinely commissioned in the

NHS in England. So, for many people, current treatment is best supportive care. The aim is to control symptoms, maintain movement and function for as long as possible, and improve quality of life. This involves a multidisciplinary approach including respiratory, gastroenterology and orthopaedic care, as well as nutritional support, physiotherapy, assistive technologies, occupational therapy and social care. However, the clinical and patient experts emphasised that these supportive treatments do not affect disease progression, so people with SMA will ultimately become dependent on their families and carers. The committee was aware of the recently published NICE highly specialised technologies guidance on onasemnogene abeparvovec for treating spinal muscular atrophy type 1. It noted that this treatment is recommended for routine commissioning for some babies 12 months or younger with SMA type 1. However, it understood that the guidance was not published at the start of this appraisal so onasemnogene abeparvovec could not be included as a comparator. The NHS England commissioning expert described the potential treatment pathway, if risdiplam were to be recommended, as a treatment option alongside nusinersen and onasemnogene abeparvovec. They explained that repeated treatment switching would only be expected in exceptional circumstances, related to issues such as fertility or side effects. The committee recognised that treatment options used routinely in the NHS in England are currently limited and there is an unmet need for people with SMA. It recalled that best supportive care is routinely used in clinical practice in the NHS in England. It concluded that best supportive care was the most appropriate comparator for risdiplam.

Clinical evidence

Evidence from SUNFISH and FIREFISH is appropriate for decision making for SMA types 1 to 3

3.5 The main clinical-effectiveness evidence for risdiplam came from 2 clinical studies:

- SUNFISH, which is a randomised, double-blind, multicentre (excluding UK sites), phase 2, placebo-controlled trial for the first 12 months of treatment. After 12 months, people in the placebo arm could switch to the risdiplam arm.

It included 180 people aged 2 to 25 years with types 2 or 3 SMA. Part 2 of SUNFISH excluded patients who had any previous treatment, and also those with type 3 SMA who were able to walk.

- FIREFISH, which is a single-arm study of 41 patients aged 1 month to 7 months with type 1 SMA and two SMN2 copies. It excluded patients who had previous treatment and those having chronic ventilation.

  There are also 2 ongoing studies. RAINBOWFISH is a phase 2, single-arm study of babies 6 weeks or younger who had been genetically diagnosed with SMA but did not have symptoms. JEWELFISH is an open-label, single-arm study for SMA types 1, 2 and 3 in people of 6 months to 60 years who had previously enrolled in the MOONFISH study or who had previously had nusinersen, onasemnogene abeparvovec or olesoxime. The ERG considered that although SUNFISH excluded patients with type 3 SMA who could walk, this group accounts for a small proportion of SMA cases. It also noted that SUNFISH and FIREFISH excluded patients who had previous treatment. The committee noted the age restrictions used in both studies. It was aware that some babies may be diagnosed with type 1 SMA when they are older than 7 months. The clinical experts explained that the study populations were generally representative of patients with SMA in the NHS in England. The committee concluded that the evidence presented for SMA types 1 to 3 was suitable for decision making.

Risdiplam may be effective for patients who have had nusinersen

3.6 After consultation the company reported interim results from JEWELFISH for 174 patients, of whom 76 had previously had nusinersen (see section 3.5). The primary outcomes for JEWELFISH were safety and pharmacokinetics, but motor function was assessed as an exploratory outcome using the 32-item Motor Function Measure (MFM-32). The 12-month interim data showed low rates of discontinuation of risdiplam for patients who previously had nusinersen, with rapid, sustained increase in SMN protein levels and stable motor function. The company stated that there is no plausible biological rationale to expect the treatment effect to differ based on prior treatment, because nusinersen and risdiplam have similar mechanisms of action (they are both SMN2 RNA splicing

modifiers). The committee recalled that some people who had nusinersen may have preferred not to have had it, but it was the only option available (see section 3.4). The company did not present any cost-effectiveness evidence for people who have had nusinersen. The committee concluded that risdiplam may be effective after previous treatments such as nusinersen and agreed to take this into account when making its recommendations.

Risdiplam may be effective for pre-symptomatic SMA

3.7 After consultation, the company reported interim results from RAINBOWFISH for 5 patients with pre-symptomatic SMA who had risdiplam for at least 12 months (see section 3.5). This 12-month interim data showed 80% of patients reached the maximum score on the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) and Hammersmith Infant Neurological Examination Module 2 (HINE-2) scales, which measure motor function. The company considered these results to be promising compared with natural history studies. For example, the ANCHOVY chart review of 60 patients, 30 of whom had confirmed SMN2 copies, suggested that no HINE-2 milestones were reached at 12-month follow up. The company highlighted that subgroup analyses from both SUNFISH and FIREFISH showed that earlier treatment improved outcomes (the company considers the data to be confidential so it cannot be reported here). The company did not present cost-effectiveness evidence for people with pre-symptomatic SMA. The committee was encouraged by early results for the pre-symptomatic SMA population and agreed to take this into account when making its recommendations.

Risdiplam improves motor function for people with SMA types 1, 2 or 3

3.8 The 12-month results from SUNFISH, adjusted for multiple testing, showed risdiplam improved motor function scores (measured by the MFM-32) in patients with type 2 or 3 SMA, compared with placebo (1.55; 95% confidence interval [CI] 0.30 to 2.81). The results from FIREFISH were compared against pre-defined performance criteria based on natural history data for patients with type 1 SMA. The 12-month results suggest that more patients who had risdiplam (29%) were

able to sit without support for at least 5 seconds than would be expected for patients with type 1 SMA (5%). After consultation, the company submitted 24-month follow-up data from both SUNFISH and FIREFISH (see table 1 and table 2). The committee noted that this longer-term data generally showed improvements or stable disease but recognised that the data was not comparative (see section 3.5). The company and the ERG agreed that improvements seen in both SUNFISH and FIREFISH were clinically important. The patient experts described their experiences of using risdiplam and noted improvements in motor function, lung capacity, energy levels and stamina. They explained that even very small improvements in fine motor skills and upper limb function were very important because they allow patients to maintain independence. They emphasised that although the studies showed improvements in motor function, patients would also highly value a treatment that keeps the disease stable and stops it getting worse. The committee agreed that the clinical evidence showed improved motor function with risdiplam but noted that overall-survival data was only available for type 1 SMA.

Table 1 Results from SUNFISH for SMA types 2 and 3. All results are mean change from baseline for risdiplam (n=120). Higher scores indicate improvement

Outcome	12-month follow up (standard deviation)	24-month follow up (standard deviation)
32-item Motor Function Measure total score	1.65 (4.70)	1.83 (5.59)
Hammersmith Functional Motor Scale Expanded total score	1.81 (3.68)	2.15 (5.28)
Revised Upper Limb Module total score	1.91 (3.87)	2.79 (4.38)
Caregiver-reported SMA independence scale score	1.68 (4.95)	2.73 (5.16)
Patient-reported SMA independence scale total score	0.95 (3.78)	0.82 (4.83)

Table 2 Results from FIREFISH for type 1 SMA. All results are for people having risdiplam (n=41). They are compared with pre-defined performance criteria, based on natural history data for patients with type 1 SMA

Outcome	12-month follow up (percentage)	24-month follow up (percentage)	Performance criterion
Sitting without support for at least 5 seconds assessed by the Bayley Scales of Infant and Toddler Development 3	12 (29%)	25 (61%)	5%
Able to support weight or stand with support as assessed by the Hammersmith Infant Neurological Examination Module 2	9 (22%)	11 (27%)	Not applicable
Able to bounce while assessing the walking item of the Hammersmith Infant Neurological Examination Module 2	1 (2%)	2 (4%)	Not applicable
Alive without permanent ventilation	35 (85%)	34 (83%)	42%
Alive	38 (93%)	38 (93%)	60%

The company's matched adjusted indirect comparison for type 1 SMA is acceptable

3.9 After technical engagement, both the company and the ERG used the company's matched adjusted indirect comparison to model the treatment effect of risdiplam compared with best supportive care for type 1 SMA. This analysis matched data from the risdiplam arm of FIREFISH and the best supportive care arm of the ENDEAR trial, which compared nusinersen with placebo. The indirect comparison showed improvements in motor function such as sitting with and without support, ventilation-free survival and overall survival (the company considers the data to be confidential so it cannot be reported here). The committee concluded that the company's matched adjusted indirect comparison for type 1 SMA was acceptable.

Long-term benefits with risdiplam are uncertain

3.10 After consultation, the company presented 24-month follow-up data from SUNFISH and FIREFISH but noted that these studies were ongoing. The ERG noted that the 24-month data for SUNFISH was not comparative because the placebo-controlled period ended after 12 months of treatment. The clinical experts explained that there was considerable uncertainty about the long-term benefits of risdiplam but in their clinical experience the results were promising. The committee concluded that risdiplam would likely provide long-term benefits, but these are uncertain because the size and nature of the benefits are not known.

The company's economic model

The company's model structure was broadly similar to the model used in the appraisal of nusinersen

3.11 The company presented 2 separate models after consultation. The model for types 2 and 3 SMA used clinical data from SUNFISH. The model for type 1 SMA used clinical data from the matched adjusted indirect treatment comparison. Both models compared risdiplam with best supportive care. Health-state transitions were based on assessments of motor milestones using the HINE-2 for type 1 SMA, and the MFM-32 and the Hammersmith Functional Motor Scale Expanded criteria for SMA types 2 and 3. After technical engagement, the company added a treatment-effect plateau similar to that used in TA588. The plateau assumed patients who have had risdiplam will not reach additional motor milestones after 66 months of treatment for SMA type 1 and 26 months for SMA type 2 or 3. The ERG explained that the company's models could be split into 3 sections:

- The first 2 years of treatment, which used data from SUNFISH and FIREFISH to determine the transition probabilities (that is, the rate that patients will move between the different health states). In the type 1 model, the company applied the inverse hazard ratio from the matched adjusted indirect treatment comparison to the risdiplam arm because FIREFISH was a single-arm study.

- After 2 years of treatment, when the transition probabilities were adjusted so disease in the best supportive care arm could not improve (it could only remain stable or worsen). The type 1 model assumed that no patients having risdiplam moved to the worse health states. The type 2 or 3 model assumed this probability was much lower for patients having risdiplam compared with best supportive care (the company considers this proportion to be commercial in confidence so it cannot be reported).
- After the treatment plateau, when the company assumed patients having risdiplam stopped treatment. After stopping risdiplam, the models assumed a gradual loss of motor milestones but there was no effect on overall survival or utility values.

  The committee concluded that the company's model was broadly similar to the model used in the appraisal of nusinersen.

The company's model structure will need to be updated at the end of the managed access period

3.12 The committee discussed several limitations of the company's models after consultation:

- The type 1 model overestimated overall survival in the best supportive care arm because it relied on using the inverse of the hazard ratio from the matched adjusted indirect treatment comparison. This overestimation increased when the updated clinical data was applied after consultation (see section 3.13).
- The model structures could not reflect the company's preferred stopping rules from NICE's updated review of TA588 because it did not allow for consecutive worsening of motor function (see section 3.17).
- The company's approach to including additional benefit from risdiplam to account for improvements in fine motor skills and fewer complications led to changes in the best supportive care arm. The committee did not consider this to be appropriate (see section 3.16).

- The model was not structured in a way that included pairs of data for patients who did and did not have risdiplam. So, it was not possible to separate out the additional overall-survival gain from risdiplam. The committee understood this affected the way that caregiver utility values were included in the model (see section 3.15).

  The committee carefully considered the limitations of the models and the new elements proposed by the company after consultation (updated data for the type 1 model, the proposed stopping rule, utility benefits from risdiplam and a new way to model caregiver utilities). It concluded that changes to the model structure were needed to calculate plausible cost-effectiveness results. The committee noted that the company committed to engaging with NHS England and the wider SMA community to propose a managed access agreement. It concluded that an updated model structure would be needed by the time the guidance is reviewed as part of the agreed managed access agreement.

Overall survival for best supportive care

The company's modelled survival for best supportive care in type 1 SMA is not appropriate

3.13 Overall-survival predictions in the type 1 model relied on the matched adjusted indirect treatment comparison because FIREFISH was a single-arm study (see section 3.5). After technical engagement, the company's model predicted a mean overall survival of 4.9 years in the best supportive care arm. The ERG noted that the company's approach overestimated overall survival in the best supportive care arm. It stated that the company should have applied the hazard ratio to the best supportive care group instead of applying the inverse of the hazard ratio to the risdiplam group. After consultation, the company updated the model with the 24-month data from FIREFISH but this led to even higher survival predictions in the best supportive care arm (10.2 years). The committee did not consider the company's approach to be appropriate because new data for risdiplam should not affect survival for patients having best supportive care. It also questioned the clinical plausibility of these assumptions. The clinical experts confirmed that the

company's model prediction did not reflect clinical practice. The committee noted that this was not an issue in the type 2 or 3 model because the best supportive care arm was modelled separately and was not changed by the updated study data. The committee concluded that the company's modelled survival for best supportive care in the type 1 model was not appropriate.

Utility values

Caregiver utility is considered in decision making but is difficult to quantify

3.14 In its original base case, the company used an additive approach and assumed that caregiver health-related quality of life increased linearly with each motor milestone that was met. The ERG explained that the company's additive approach assumed that after a patient died the caregiver health-related quality of life was zero. This increased the quality-adjusted life year (QALY) gains for risdiplam because patients live longer. The ERG did not think this was appropriate because it assumed society places value on caregivers of patients with SMA but not on bereaved caregivers after a patient dies. Submissions at technical engagement from patient and professional organisations emphasised that bereavement would have a significant and sustained effect on a caregiver's health-related quality of life. After technical engagement, the ERG presented its preferred analysis and 2 scenario analyses that explored the effects of bereavement. It preferred to apply a disutility (reduction in health-related quality of life) that was linked to the health state of the patient with SMA. But in the base case, after the patient died, the caregiver utility value was assumed to return to that of the general population. In the first scenario, the ERG applied a disutility of -0.04 from Song et al. (2010) for 20 years after a patient with SMA died. In the second scenario the same disutility was applied for the maximum time horizon (90 years). The ERG cautioned that the analyses were limited because they used arbitrary assumptions and the company's model did not include caregiver ageing or survival. The committee considered that the ERG's disutility approach:

- was consistent with TA588, and it was not aware of any previous technology appraisals that used the company's preferred additive approach to model

caregiver utility values

- did not fully account for the effect of bereavement on caregiver quality of life. It noted that NICE's guide to the methods of technology evaluation states that direct health effects for carers can be included in analyses, but it is unclear whether this extends to valuing caregiver bereavement

- substantially increased the cost-effectiveness estimates, particularly for type 1 SMA. This was because the substantial caregiver disutilities were subtracted from the patient utility values, which themselves reflect a poor quality of life. So increased survival results in a low number of QALYs, but at a high extra cost. This was less of an issue for type 2 and type 3 SMA because the additional survival is associated with higher patient utility and lower carer disutility than in the type 1 model, meaning a higher number of QALYs can be accrued. The company noted that this was counterintuitive because it made a life-extending treatment appear to be less cost effective. It also noted that using the ERG's approach meant that risdiplam was not cost effective, even when there was no cost for risdiplam. The ERG explained that the cost effectiveness of risdiplam was related to other factors including extended overall survival and high disease management costs. Also, the committee understood that the company preferred to assume each patient with SMA would have 2.2 caregivers. However, the ERG preferred to assume 3 caregivers for patients with type 2 or 3 SMA who cannot sit because this is consistent with TA588.

  The committee did not accept the company's approach to caregiver utility but recognised the difficulties in valuing caregiver utility values. It noted that the ERG approach also had limitations and resulted in particularly high incremental cost-effectiveness ratios (ICERs) for type 1 SMA. Despite accepting the logic of the ERG's modelling, it did not agree that including carer quality of life would result in fewer QALYs being accrued by carers when risdiplam extends survival. The committee concluded that the ERG's approach to including caregiver utility values is consistent with TA588 but neither the company's nor the ERG approach was ideal. The committee concluded that it should consider carer utility in its decision making but that quantifying caregiver utility was extremely difficult.

The company's amended approach to modelling caregiver utilities for type 1 SMA is not appropriate

3.15 After consultation, the company used the ERG's disutility approach to include caregiver utility values for patients with type 2 or 3 SMA. For patients with type 1 SMA, the company used an amended disutility approach in which:

- a disutility was applied to both treatment groups until 10.2 years (the mean overall survival for the best supportive care arm)
- there were no QALY losses applied after this time, and
- an additional bereavement disutility was applied to both arms until mean overall survival was reached (about 31 years for risdiplam).

The company explained that this approach addressed the committee's concerns at the first meeting because it did not include caregiver QALY losses for risdiplam from extending survival. The ERG noted that in the company's approach, the total caregiver QALY losses over time were similar for each treatment group although the reasons differed. In the risdiplam group, QALY losses were driven by patients being in better health states and more patients surviving. In the best supportive care group, QALY losses were driven by patients being in worse health states and fewer patients surviving. The ERG recognised that including caregiver utility values in the economic model was challenging, particularly for type 1 SMA, because risdiplam extended overall survival and this led to increased caregiver burden over this extended period. But it did not consider the company's approach to be appropriate because:

- it is inconsistent to assume SMA affects caregivers up to a specific timepoint but not beyond it
- the company's cohort-level model did not include data for pairs of patients having risdiplam and those who were having best supportive care, so it was not possible to determine the additional extension to life from risdiplam, and
- QALY losses in the best supportive care arm were also affected and this was counterintuitive.

The committee discussed the challenges of including caregiver utility values in the economic model. It noted that the company's approach for type 1 SMA was limited by the model structure and its predictions may not be clinically plausible. It would have liked to have seen caregiver utility values fully captured in the model, a consideration of the impact of bereavement and the same approach used for both models. It concluded that the company's amended approach for including caregiver utility values for type 1 SMA was not appropriate.

The company's approach to account for risdiplam's additional benefits is not appropriate

3.16 After technical engagement, the company included in its base case an additional utility gain to reflect risdiplam's potential benefits in fine motor skills. The company applied a utility gain of 0.05 and 0.10 for patients who had risdiplam in the non-sitting and sitting health states respectively, based on Thokala et al. (2020). The ERG preferred to exclude these additional utility gains for fine motor skills because:

- the values were based on assumptions rather than evidence
- there was uncertainty about how many patients who had risdiplam would have these utility gains, and
- there was uncertainty about the duration of any utility gains.

The patient experts described the importance of maintaining upper limb function because it allows independence. They explained that some benefits were not captured in the available motor function scales because even small improvements were highly valued by patients and made a large difference to health-related quality of life. The committee was sympathetic to these arguments and noted that 24-month follow-up data from SUNFISH showed improvements in upper limb function and SMA independence scale scores (see table 1). After consultation, the company increased the size of the additional benefit for fine motor skills. It explained that clinical and patient advice suggested that quality of life could improve by about 50%. So, it

increased utility values by 0.2 for patients in all sitting and non-sitting health states and by 0.05 for caregivers. The company also amended the utility values to try and account for benefits of risdiplam that may not be captured in the modelling. It did this by applying additional disutility values and costs for scoliosis and decline in respiratory and bulbar function (including swallowing, vocalising and communication). The ERG highlighted several limitations of the company's approach, which applied costs and disutility values to all patients in the best supportive care arm and 50% of patients in the risdiplam arm:

- The company's assumptions may not be clinically plausible because additional utility gains were maintained even after risdiplam was stopped.
- Double counting may be an issue because the original utility estimates from TA588 came from an elicitation study of clinical experts. The ERG considered that these factors could already be accounted for in the estimated patient utility values for the best supportive care group.
- The company's net utility values may not be plausible after accounting for additional benefits from fine motor skills and fewer complications. Also, the changes should not have impacted net values for the best supportive care arm.

The committee considered that an elicitation approach, similar to that used in TA588, may provide more robust estimates of net utility values. It would have liked to have seen:

- plausible utility values elicited from clinical and patient experts for each health state for both treatment groups
- consideration of which patients might accrue these benefits and for how long after stopping treatment.

The committee concluded that the company's approach to account for risdiplam's additional benefits was not appropriate, because it resulted in health-state values in each arm that were not plausible.

Stopping rule for risdiplam

Analyses based on the company's modelled stopping rules are not appropriate

3.17 After consultation, the company amended its time-based stopping rule for risdiplam, which restricted its use to a maximum of 50 years for type 1 SMA and 30 years for types 2 and 3 SMA. It applied criteria to stop risdiplam in the worst health states after the treatment plateau (see section 3.11). The company explained that if the committee conclude it is appropriate to include stopping rules in its recommendations, it would prefer that these align with the stopping rules from NICE's updated review of TA588. However, these rules cannot be included within the current model structures. So, it used the treatment plateau as a proxy instead but acknowledged that the rules that were applied in the economic models would not be used in clinical practice. The committee understood that the updated stopping criteria in TA588 were based on clinical outcomes including repeated loss of motor function, the need for ventilation and scoliosis. The patient and clinical experts advised that the updated criteria were developed in collaboration with the wider SMA community. The new criteria allowed greater flexibility on the scales used to measure motor function and had generally been accepted by the clinical and patient community. The ERG explained that the stopping rule used in the models assumed lower costs for risdiplam but there was no change to predicted overall survival and predicted additional benefits from fine motor skills and lower rates of complications. The committee did not consider it appropriate to assume that the benefits of risdiplam would continue after treatment stopped. It was also concerned that the stopping rule modelled by the company did not reflect clinical practice. The clinical and patient experts reiterated that a treatment plateau is considered a positive outcome because it suggests disease is stable and would not be a reason to stop treatment. The committee would have liked to have seen the company's intended stopping rule applied to the models. It noted that an amended model structure that allowed consecutive worsening of motor function would be needed as well as consideration of the plausibility of sustained benefits after treatment is stopped. The committee concluded that analyses based on the company's modelled stopping rules were not appropriate for decision-making.

End of life

It is reasonable to accept that risdiplam meets the short life-expectancy criterion for type 1 SMA

3.18 The committee considered the advice about life-extending treatments for people with a short life expectancy in NICE's guide to the methods of technology appraisal. The company proposed that risdiplam met NICE's criteria for a life-extending treatment at the end of life for type 1 SMA, but did not make a case for meeting the criteria for SMA types 2 and 3. The committee accepted that risdiplam did not meet the end-of-life criteria for people with type 2 or 3 because, although risdiplam may provide a survival benefit, life expectancy is likely to be over 2 years. For people with type 1 SMA the company noted that survival depends on the nature and extent of supportive care. The median age of death or permanent respiratory support in published natural history studies was 9 months to 13 months. The ERG commented that mean survival in the company's model for people with type 1 SMA having best supportive care was 4.88 years, but this was likely to be overestimated because of the way the company had applied the hazard ratios in the model (see section 3.13). The committee recalled that, after consultation, the company's model for type 1 SMA predicted mean overall survival of 10.2 years in the best supportive care arm. The committee did not consider this to be clinically plausible (see section 3.13). It noted that it usually assesses whether this criterion is met by referring to the mean survival predicted by the model. However, it accepted the limitations of the model in this case mean that estimates from the literature are more robust. The committee recognised that the life expectancy is uncertain but considered it reasonable to accept that risdiplam could meet the short life-expectancy criterion for type 1 SMA.

It is likely that risdiplam extends life by more than 3 months for type 1 SMA

3.19 Having concluded that the short life-expectancy criterion was met for type 1 SMA, the committee recalled that the long-term survival estimates for these patients are very uncertain (see section 3.10). However, the modelling suggests

that risdiplam is likely to extend life by at least 3 months for type 1 SMA. The committee noted that nusinersen (TA588) was considered to have met the criteria for a life-extending treatment at the end of life for type 1 SMA, but not for types 2 or 3. The committee concluded this also applied for risdiplam.

Cost-effectiveness results

The ICERs for risdiplam are above £50,000 per QALY gained

3.20 After consultation, the company's base-case ICERs for risdiplam compared with best supportive care were below £30,000 per QALY gained for SMA types 2 and 3 but were above £50,000 per QALY gained for SMA type 1 (the company considers the exact ICERs to be confidential so they cannot be reported here). The committee noted that the company's analyses did not include all of its preferred assumptions, and concluded that:

- The company's modelled stopping rules are not appropriate (see section 3.17).
- The company's approach to account for risdiplam's additional benefits is not appropriate (see section 3.16).
- The ERG's approach for including caregiver utility values is accepted because it is consistent with TA588 but there is substantial uncertainty (see section 3.14).
- For type 1 SMA, the company's amended disutility approach to include caregiver utility values is not appropriate (see section 3.15).

  The committee noted that, using its preferred assumptions, the most plausible ICER for type 1 SMA is likely to be much higher than £50,000 per QALY gained. For types 2 and 3, the ICER was much higher than £30,000 per QALY gained. The committee also recalled that after consultation the company's model structure led to implausible predictions for the best supportive care arm and did not allow clinically appropriate stopping rules based on consecutive worsening to be implemented (see section 3.11 and section 3.17). Also, it affected how caregiver utility values were included (see

section 3.15). The committee concluded that the ICERs for risdiplam are likely to be above £50,000 per QALY gained but that changes to the model structure are needed to robustly capture all the costs and benefits associated with risdiplam.

Other factors

A managed access agreement has the potential to address uncertainties

3.21 The committee noted that the company engaged with NHS England and Improvement, the patient and clinical community and NICE to develop a managed access agreement for risdiplam. The agreement includes defined criteria for starting and stopping risdiplam, and for monitoring and data collection requirements. The proposed managed access agreement includes people with SMA types 1 to 3 as well as pre-symptomatic SMA. The committee recalled that it was encouraged by the early results from RAINBOWFISH (see section 3.7) and agreed that it was appropriate that pre-symptomatic SMA should be included within a managed access agreement and further data collected. It also acknowledged the need to manage risks associated with the identified uncertainties. It considered the details of the proposed eligibility criteria in the managed access agreement and concluded that they were clinically achievable. It considered that the proposed commercial agreement would reduce the risk to the NHS while the data was being collected. The committee concluded that the uncertainties in risdiplam's clinical evidence could be addressed by collecting data through a managed access agreement.

Risdiplam is innovative and there may be some benefits not captured in the models

3.22 The company suggested that risdiplam is innovative because it is taken orally, so people can have treatment at home. The clinical and patient experts explained that nusinersen is given by lumbar puncture. Many people with SMA have spinal

fusion, which means they cannot have a lumbar puncture so are unable to have nusinersen. The clinical and patient experts agreed that an alternative treatment option is needed. The company suggested that the models do not adequately reflect all potential benefits of risdiplam. This is because the benefits of improvements in respiratory and bulbar function (such as swallowing, vocalising and the ability to communicate) may not have been adequately captured in the models. The committee noted that even small improvements in motor skills are highly valued by patients and make a large difference to health-related quality of life, which may not be captured in the available motor function measures (see section 3.16). After consultation, the company attempted to include the uncaptured benefits of risdiplam in its modelling. The committee did not consider the company's approach to be plausible (see section 3.16) so preferred not to base its decision making on these analyses. It agreed that risdiplam was innovative and that there may be some benefits not captured in the models.

No equality issues were identified

3.23 The patient and professional submissions suggested that the use of arbitrary disease categories means some people with type 3 SMA cannot access other treatments. The committee discussed this and recognised the limitations but noted that these classifications are used in the marketing authorisation and the clinical evidence. A clinical expert commented that the evidence did not fully capture the diverse ethnic demographic of people with SMA. The committee considered these potential issues but noted that recommendations would apply to all patients, regardless of ethnicity. It concluded that no equality issues had been identified.

The nature of the eligible population and the disease was considered in the decision making

3.24 The committee noted that the population for which risdiplam is indicated includes children and young people. It noted that the clinical evidence and the models included children affected by the condition. It discussed whether adjustments to its normal considerations were needed. It discussed the need to balance the importance of improving the lives of children and their families with fairness to

people of all ages. It noted NICE's principles for the development of guidance and standards, which emphasise the importance of considering the distribution of health resources fairly within society as a whole, as well as factors other than relative costs and benefits. The committee acknowledged that the population eligible for risdiplam has serious disabilities. It acknowledged and considered the nature of the eligible population as part of its decision making.

The decision making takes into account the rarity and severity of the disease

3.25 Risdiplam has features that are commonly seen in treatments assessed by NICE's highly specialised technologies programme, but it was considered as a single technology appraisal. This is because the population covered by the marketing authorisation is larger than what can be considered in highly specialised technologies evaluations. Also, the management of SMA is not commissioned through a highly specialised service. The committee acknowledged the difficulty of appraising drugs for very rare conditions. The committee was aware that SMA is a rare and very serious condition. It reflected on the benefits associated with risdiplam, and how they are highly valued by patients and families. It acknowledged and considered whether adjustments to its normal considerations were needed to take into account the rarity and severity of the disease. Its decision making took into account the rarity and severity of the disease.

Conclusion

Risdiplam is recommended for treating SMA with a managed access agreement

3.26 The committee acknowledged that the cost-effectiveness estimates were above the range NICE normally considers cost effective. However, it was mindful of many other important factors to account for in its decision making. It recalled that there were benefits associated with risdiplam that may not have been captured in the economic analyses. It also recognised that there is evidence of benefit for those who have had previous treatment and pre-symptomatic SMA (see section

3.6 and section 3.7). It also acknowledged the difficulty in distinguishing between SMA types (see section 3.2). However, the committee acknowledged that all the clinical- and cost-effectiveness evidence presented was uncertain, because of the lack of data. It accepted that more data was needed, and considered that the commercial agreement sufficiently manages the financial risk to the NHS. The committee considered the consultation responses, views of parents, carers and clinical experts, and the available evidence. It concluded that risdiplam should be recommended as an option for treating pre-symptomatic SMA and SMA types 1, 2 and 3, for the duration of and within the conditions set out in the managed access agreement. This is only if the company provides risdiplam with the confidential commercial terms agreed with NHS England. It reiterated that an updated model structure should be provided when the guidance is reviewed as part of the agreed managed access agreement.

4 Implementation

4.1 When NICE recommends a treatment as an option for use within a managed access agreement, NHS England will make it available according to the conditions in the managed access agreement. This means that, if a person has types 1, 2 or 3 spinal muscular atrophy (SMA) or pre-symptomatic SMA with 1 to 4 SMN2 copies, and the doctor responsible for their care thinks that risdiplam is the right treatment, it should be available for use, in line with NICE's recommendations and the criteria in the managed access agreement.

4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance when the drug or treatment, or other technology, is approved for use within a managed access agreement. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, for use within a managed access agreement, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document or agreement of a managed access agreement by the NHS in Wales, whichever is the later.

5 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee C.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Abitha Senthinathan
Technical lead

Alex Filby
Technical adviser

Louise Jafferally
Project manager

Update information

December 2023

The Medicines and Healthcare products Regulatory Agency approved a licence extension for risdiplam to include people of all ages (previously 2 months and over). We updated the recommendation and information in section 2 to account for this extension to the marketing authorisation.

ISBN: 978-1-4731-5642-5