NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Risdiplam for treating spinal muscular atrophy

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using risdiplam in the NHS in England. The appraisal committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, clinical experts and patient experts.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the consultees and commentators for this appraisal and the public. This document should be read along with the evidence (see the committee papers).

The appraisal committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The appraisal committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the committee will also consider comments made by people who are not consultees.
- After considering these comments, the committee will prepare the final appraisal document.
- Subject to any appeal by consultees, the final appraisal document may be used as the basis for NICE's guidance on using risdiplam in the NHS in England.

For further details, see NICE's guide to the processes of technology appraisal.

The key dates for this appraisal are:

Closing date for comments: 23 June 2021.

Second appraisal committee meeting: 13 July 2021.

Details of membership of the appraisal committee are given in section 5.

1 Recommendations

1.1 Risdiplam is not recommended, within its marketing authorisation, for treating 5q spinal muscular atrophy (SMA) in people 2 months and over, with a clinical diagnosis of SMA types 1, 2 or 3 or with one to four SMN2 copies.

1.2 This recommendation is not intended to affect treatment with risdiplam that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop. For children and young people, this decision should be made jointly by the clinician and the child/young person and/or their parents or carers.

Why the committee made these recommendations

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

There is no evidence on risdiplam for babies with pre-symptomatic SMA. Clinical evidence shows that risdiplam improves motor function in SMA types 1 to 3. Also, there is some evidence suggesting that people with type 1 SMA who have risdiplam live for longer. But there is no direct evidence comparing risdiplam with best supportive care for type 1 SMA. And there is no long-term evidence, so the estimated long-term benefits are highly uncertain.

The committee considered a wide range of issues in its decision-making. In particular, it discussed the rarity and severity of SMA, risdiplam's innovative oral administration, uncertainties in the evidence, and whether risdiplam should be considered as an end-of-life treatment.

The cost-effectiveness estimates presented are much higher than what NICE usually considers an acceptable use of NHS resources. So, even taking these other factors into account, risdiplam cannot currently be recommended.

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 2 months of age and older, with a clinical diagnosis of SMA Type 1, Type 2 or Type 3 or with one to four SMN2 copies'.

Dosage in the marketing authorisation

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

Price

2.3 The list price is £7,900 per 60mg/80ml vial. The company has a commercial arrangement, which would have applied if the technology had been recommended.

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:

- There is no clinical evidence for risdiplam in people who have had previous treatment (such as nusinersen) or have pre-symptomatic disease (see key issue 1 in the ERG report, page 13).
- The company's unanchored matched adjusted indirect comparison of risdiplam with best supportive care is acceptable. But applying the hazard ratio from the matched adjusted indirect comparison may overestimate overall survival in the best supportive care arm (see key issue 2 in the ERG report, page 15).

- The company's treatment-effect plateau (which assumes patients who have had risdiplam will not reach additional motor milestones after 66 months for type 1 SMA and 26 months for SMA types 2 or 3) is acceptable and consistent with NICE's technology appraisal of nusinersen for treating spinal muscular atrophy (TA588) (see key issues 3, 6 and 7 in the ERG critique of the company's technical engagement response, page 12).
- The company's patient utility values are acceptable (see key issue 8 in the ERG critique of the company's technical engagement response, page 14).
- The company's model is reasonably consistent with TA588 (see key issue 9 in the ERG critique of the company's technical engagement response, page 14).

It discussed the following issues (issues 4, 5 and 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 at some point, 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 will 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 it 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 and 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 is the only disease-modifying treatment currently available for SMA. The clinical and patient experts explained that many people with SMA have spinal fusion 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 and 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 NICE's guidance 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, current treatment for many people 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 an ongoing highly specialised technology evaluation for onasemnogene abeparvovec for treating spinal muscular atrophy type 1. It was aware that this treatment was recommended in draft guidance for routine commissioning for some babies 12 months or younger with SMA type 1. However, it understood that the guidance was not final and therefore 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. It included 180 people aged 2 to 25 years with types 2 or 3 SMA. Part 2 of this study excluded patients who had any previous treatment and 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 (see section 3.6). 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.

There is no clinical or cost-effectiveness evidence for patients who have had nusinersen

3.6 The company did not present any clinical or cost-effectiveness evidence for people who have had nusinersen. The committee recalled that the ongoing JEWELFISH study was relevant but noted that the company had not presented any interim results from this study (see section 3.5). The company stated that there is no plausible biological rationale to expect the treatment effect to differ based on prior treatment because both nusinersen and risdiplam have a similar mechanism of action (they are both SMN2 RNA splicing modifiers). The committee recalled that some people who have had nusinersen may have preferred not to have it but it was the only option available (see section 3.4). The committee concluded

that it had not seen any evidence for people who have had nusinersen and agreed to take this into account when making its recommendations.

There is no evidence for patients with pre-symptomatic SMA

3.7 The company did not present any clinical or cost-effectiveness evidence for people with pre-symptomatic SMA. The committee noted that the ongoing RAINBOWFISH study was relevant but the company had not presented any interim results from this study (see section 3.5). 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 committee concluded that it had not seen any evidence for people who had pre-symptomatic SMA 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 results from SUNFISH, adjusted for multiple testing, showed risdiplam improved motor function scores (measured by the Motor Function Measure, 32 items) and fine motor skills (measured by the Revised Upper Limb Module) in patients with type 2 or type 3 SMA, compared with placebo (see table 1). The results from FIREFISH were compared against pre-defined performance criteria, based on natural history data for patients with type 1 SMA. The results (see table 2) suggest that after 12 months of treatment with risdiplam, more patients were able to sit without support for at least 5 seconds than would be expected for patients with type 1 SMA. Overall survival was 93% (90% confidence interval 82.2% to 97.1%). 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. 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 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, they 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 were only available for type 1 SMA.

Table 1 Results from SUNFISH for SMA types 2 and 3 at 12-month follow up

Outcome	Risdiplam n=120 (SE)	Placebo n=60 (SE)	Difference, risdiplam minus placebo (95% CI)	p-value
MFM-32 total Score	1.36 (0.38)	–0.19 (0.52)	1.55 (0.30 to 2.81)	0.02*, 0.02**
HFMSE total Score	0.95 (0.33)	0.37 (0.46)	0.58 (–0.53 to 1.69)	0.39*, 0.30**
RULM total Score	1.61 (0.31)	0.02 (0.43)	1.59 (0.55 to 2.62)	0.05*, 0.00**
Caregiver-reported SMAIS score	1.65 (0.50)	–0.91 (0.67)	2.55 (0.93 to 4.17)	0.39*, 0.00**
Patient-reported SMAIS total score	1.04 (0.65)	–0.40 (0.86)	1.45 (–0.68 to 3.57)	0.18

Table note: All data are least squares mean change from baseline. Higher scores indicate improvement. *adjusted for multiple testing **unadjusted. Table abbreviations: CI, confidence interval; HFMSE, Hammersmith Functional Motor Scale Expanded; MFM-32, Motor Function Measure - 32 items; RULM, Revised Upper Limb Module; SE, standard error; SMAIS, SMA independence scale.

Table 2 Results from FIREFISH for type 1 SMA at 12-month follow up

Outcome	Risdiplam n=120 Number and proportion (90% CI) of patients	Performance criterion
Sitting without support for at least 5 seconds (BSID-III)	12/41, 29.3% (17.8 to 43.1%)	5%
Able to support weight or stand with support as assessed by the HINE-2	9/41, 22.0% (12.0 to 35.2%)	N/A
Able to bounce while assessing the walking item of the HINE-2	1/41, 2.4% (0.1 to 11.1%)	N/A
Alive without permanent ventilation	35/41, 85.4% (73.4 to 92.2%)	42%
Alive	38/41, 92.7% (82.2 to 97.1%)	60%

Table note: The results from FIREFISH were compared against pre-defined performance criteria, based on natural history data for patients with type 1 SMA.
Table abbreviations: BSID-III, Bayley Scales of Infant and Toddler Development; CI, confidence interval; HINE-2, Hammersmith Infant Neurological Examination Module 2.

Long-term benefits with risdiplam are uncertain

3.9 The company presented 12-month follow-up data from SUNFISH and FIREFISH but noted that these studies were ongoing. The ERG noted further data for SUNFISH would not be comparative because the placebo-controlled period ended after 12 months. 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, although risdiplam would likely provide long-term benefits, the size and nature of these benefits are not known so this is uncertain.

The company's economic model

The company's models are acceptable for decision making

3.10 The company presented 2 separate models: the types 2 and 3 SMA model used clinical data from SUNFISH and 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 Hammersmith Infant Neurological Examination Module 2 for type 1 SMA, and the 32 item Motor Function Measure and the Hammersmith Functional Motor Scale Expanded criteria for SMA types 2 and 3. In the type 1 model, the ERG noted that the company's approach overestimates 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 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 for SMA type 1 and 26 months for SMA type 2 or 3. The ERG explained that the company's models were broadly consistent with the final model used in TA588 but there were differences in the stopping rule and caregiver assumptions (see sections 0 and 3.13). The committee concluded that the company's models were acceptable for decision making.

Stopping rule for risdiplam

The company's stopping rules may not be appropriate

3.11 After technical engagement, the company included a stopping rule for risdiplam. This restricted its use to a maximum of 50 years for type 1 SMA and 30 years for types 2 and 3 SMA. The committee noted that this approach differed to the stopping criteria in TA588, which was based on clinical outcomes including repeated loss of motor function, the need for ventilation and scoliosis. Clinical advice to the company suggested that a time-based rule may be easy to implement in the NHS in England and may be preferred to the current criteria set out in TA588 because it would avoid pressure for continuous motor milestone improvement. The clinical and patient experts agreed that the current stopping rules in TA588 were problematic and put undue strain on patients and their caregivers. The

clinical expert suggested that a maximum treatment duration of 50 years would be reasonable for type 1 SMA, but 30 years may not be appropriate for types 2 and 3. This is because many adults may still benefit from risdiplam and it would be unfair to stop treatment for these people. The ERG preferred not to include the company's time-based stopping rule because it was not based on any evidence. But it noted that a stopping rule based on clinical criteria may improve risdiplam's cost-effectiveness. The clinical and patient experts agreed that the stopping rule used in TA588 is challenging to implement in clinical practice. So, the committee considered that appropriate stopping criteria should be explored in collaboration with clinical and patient experts and the wider SMA community. It was aware that there is ongoing work reviewing the TA588 stopping criteria for nusinersen and agreed that this could also be relevant for risdiplam. In the absence of updated criteria from TA588, the committee concluded that the company's stopping rules may not be appropriate and it would like to see stopping rules based on clinical criteria that have been agreed with clinical and patient experts.

Utility values

The company's utility gain for fine motor skills is acceptable but there is uncertainty around the exact value and the benefit could be larger

3.12 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 treated with risdiplam in the non-sitting and sitting health states respectively, based on Thokala et al. (2010). 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 around how many patients treated with risdiplam would have these utility gains
- there was uncertainty around 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 SUNFISH showed improvements in upper limb function at 12 months and also in the SMA independence scale (see table 1). It concluded that the company's utility gain for fine motor skills is acceptable but there is uncertainty around the exact value and the benefit could be larger.

The ERG's approach to including caregiver utility values is consistent with NICE's appraisal of nusinersen but there is substantial uncertainty

3.13 Both the company and ERG included caregiver-related utility values but their approaches differed. 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 surviving patients with SMA but does not for bereaved caregivers. 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 the patient with SMA died and 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 understood that the ERG's disutility approach was consistent with TA588 and was not aware of any previous technology appraisals that used the company's preferred additive approach to model caregiver utility values. It also noted that while the guide to the methods of technology evaluation states that when relevant, direct health effects for carers can be included in analyses, it is unclear whether this extends to valuing caregiver bereavement. It recalled that SMA has a substantial effect on carers and families as well as patients and can affect multiple members of the extended family (see section 3.3). It was aware that using the ERG's preferred disutility approach substantially increased the cost-effectiveness ratios, 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. Therefore, it would welcome suggestions for alternative approaches for valuing caregiver quality of life in this appraisal. 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 is ideal, so there is substantial uncertainty.

End of life

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

3.14 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 in the type 2 and 3 population because, although risdiplam may provide a survival benefit, life expectancy was likely to be over 2 years. For type 1 SMA, the company noted that survival depends on the nature and extent of supportive care. This may vary by country, NHS trust, clinician, and the preferences of patients and their families. 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 an overestimate because of the way the company had applied the hazard ratios in the model (see section 3.10). The committee noted that it usually prefers to assess 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

3.15 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 3.9). 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

3.16 The company's base-case ICERs for risdiplam compared with best supportive care were above £50,000 per QALY gained for SMA types 1, 2 and 3 (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 stopping rules may not be appropriate (see section 3.11).
- The company's utility gain for fine motor skills is acceptable but may be too low (see section 3.12).
- The ERG's approach for including caregiver utility values is accepted because it is consistent with TA588 but there is substantial uncertainty (see section 3.13).

The committee noted that, using its preferred assumptions, the most plausible ICER for type 1 SMA was 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 company considers the ICERs to be confidential so they cannot be reported here). The committee concluded that the ICERs for risdiplam are above £50,000 per QALY gained.

Other factors

There could be some benefits that are not captured in the models

3.17 The company suggested that the models do not adequately reflect all potential benefits of risdiplam 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 3.12). It noted that its preferred assumptions included an additional utility gain for fine motor skills but agreed that this benefit could be larger. The committee concluded that there could be some benefits that are not captured in the models.

Risdiplam is innovative

3.18 The company suggested that risdiplam is innovative because it provides an oral treatment option for people who cannot have nusinersen and also allows people to 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 committee concluded that risdiplam is innovative, but no data had been presented for benefits relating to its innovative nature that had not already been captured in the economic analyses.

No equality issues were identified

3.19 The patient and professional submissions suggested that the use of arbitrary disease categories means some patients with SMA (adults and 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

3.20 The committee noted that the population for which risdiplam is indicated includes children and young people, and that children being affected by the condition was captured in the clinical evidence and the models. It discussed whether any 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 the principles that guide the development of NICE 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

3.21 Risdiplam has features that are commonly seen in treatments assessed by the 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, and because the management of patients with 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 both rare and a very serious condition. It also reflected on the benefits associated with risdiplam, and how they are highly valued by patients and families. It acknowledged and considered whether any adjustments to its normal considerations were needed to take into account the rarity and severity of the disease. The decision making takes into account the rarity and severity of the disease.

Conclusion

Risdiplam cannot be recommended at this time because it is not likely to be a cost-effective use of NHS resources for treating SMA types 1 to 3

3.22 The committee acknowledged that the end of life criteria are met but, using its preferred assumptions (see section 3.16), the most plausible ICER for type 1 SMA was 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 company considers the ICERs to be confidential so they cannot be reported here). The committee acknowledged the following uncertainties:

- caregiver utility values were a key model driver, particularly for type 1 SMA. There are methodological challenges and uncertainty associated with this. The counterintuitive results in the type 1 model meant that a life-extending treatment was considered less cost effective when including caregiver utilities (see section 3.13)
- the matched adjusted indirect comparison overestimated survival for best supportive care, which means that the cost-effectiveness results could be even higher (see section 3.10)
- the benefits of risdiplam may not have been fully captured in the modelling (see section 3.17).

The committee also acknowledged other factors including the innovative nature of risdiplam, the nature of the eligible population and the rarity and severity of SMA (see sections 3.18 to 3.21). Taking all this into account, the committee concluded that risdiplam is not likely to be a cost-effective use of NHS resources for treating SMA. It noted that the company had not submitted a proposal for a managed access agreement and concluded that risdiplam cannot be recommended for routine commissioning in the NHS at this time.

4 Proposed date for review of guidance

4.1 NICE proposes that the guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Stephen O'Brien
Chair, appraisal committee
May 2021

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

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