Risdiplam for treating spinal muscular atrophy in children and adults [ID1631]

Consultation on the appraisal consultation document – deadline for comments by 5pm on Wednesday 23 June 2021. To be submitted via NICE DOCS.

Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly.

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 provisional recommendations sound and a suitable basis for guidance to the NHS?

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations:
- could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology;
- could have any adverse impact on people with a particular disability or disabilities.

Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced.

<table>
<thead>
<tr>
<th>Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):</th>
<th>[SMA UK and MDUK]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.</td>
<td>[Neither organisation has past or current direct or indirect links to, or funding from, the tobacco industry]</td>
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<tr>
<td>Name of commentator person completing form:</td>
<td>[Liz Ryburn]</td>
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<tr>
<td>Comment number</td>
<td>Comments</td>
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<tr>
<td>Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.</td>
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### Example 1

We are concerned that this recommendation may imply that …………..

### 1

We are disappointed by NICE’s initial ‘no’ to recommending risdiplam for NHS funding.

### 2

Has all of the relevant evidence been taken into account?

NICE’s summary indicates that the committee heard, and has taken into account, the evidence put forward by clinical and patient experts. We welcome this. Please see further related responses in comments 3 - 6.

### 3

**The classification system discussion**

‘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’. (3.2)

We hope that, for all the reasons stated in our original submission and presented at the ‘NICE Review of access for those with SMA Type 3 to nusinersen’, this conclusion confirms that if risdiplam is finally recommended, there will not be any barrier to access based on the clinical classification SMA Type 1, 2 or 3 of a child, young person or adult’s SMA.

### 4

**The impact of SMA**

‘The committee concluded that SMA has a substantial effect on the quality of life of patients, caregivers and their families’. (3.3)

We are pleased that this patient group evidence has been heard and is considered. We note however, that there remains a debate over caregiver QALYs – please see 13. below.

### 5

**Risdiplam is an Innovative treatment that will meet an unmet need**

Patient groups,

‘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.’ (3.4)

‘supportive treatments do not affect disease progression, so people with SMA will ultimately become dependent on their families and carers’. (3.4)

‘treatment options used routinely in the NHS in England are currently limited and there is an unmet need for people with SMA1’ (3.4)

As described in all submissions from patient and clinical experts, a treatment that may be administered at home is a hugely important option. It avoids the costs and logistical challenges to adults and families with children of regular, lifelong travel for treatment. It also eliminates the need for a particularly invasive procedure that is not possible for many with SMA.

### 6

**The future possibility of switching between treatments**

‘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.’ (3.4)
We were pleased to hear this open discussion and that the need for this possibility has been acknowledged.

If risdiplam is recommended, we would ask however that the following is taken into account:

‘The committee recalled that some people who have had nusinersen may have preferred not to have it, but it was the only option available’ (3.4)

The committee also noted that ‘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).’ (3.6)

If risdiplam is recommended, we would want all those currently receiving nusinersen to have discussions with their clinical team and the opportunity of switching treatment and, unless there is a clinical safety issue, the possibility of a switch.

We hope that the company’s assurance as above and the trust we have in our clinical colleagues will mean that the committee’s comment that it ‘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’ (3.6) would not prevent such a recommendation.

We hope that the company’s comment above that was noted by the committee, will provide sufficient evidence to support switching in any of the circumstances described in this section.

7  Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Clinical effectiveness (see 8 - 9)

8  Clinical trials

The summaries of the clinical trials provide the base case for NICE. We note the SUNFISH age criteria of 2 – 25 years and that the study excluded patients clinically classified as SMA type 3 SMA who were able to walk. We would be concerned if the lack of evidence for this group were to lead the committee to conclude that this group should be excluded for access to treatment. We reiterate this comment from our survey respondent included in our original submission that summarises the progressive nature of this condition:

“The diagnosis needs to be as dynamic as the condition…The etymology of the disease dictates that wherever people start on the continuum of SMA they are on an ever-decreasing scale. As such if you start as a type 3 or type 2 eventually those people have the same end point.”

We note that FIREFISH - 41 patients aged 1 month to 7 months with type 1 SMA and two SMN2 copies, excluded patients who had previous treatment and those having chronic ventilation. We are keen for clinicians to comment to NICE as to whether these exclusions would be appropriate in the real world setting and for NICE to hear and respond to this.

We are also keen for assurance that these criteria would not be used for others seeking this treatment. We are aware there was no restriction on ventilation support for the risdiplam EAMS and know of two adults, unable to access nusinersen, who would not be able to access treatment if this was a criterion for exclusion. They have both been relieved to be...
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<table>
<thead>
<tr>
<th>9</th>
<th><strong>Real world evidence</strong></th>
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<tbody>
<tr>
<td>We are pleased to see that the committee noted, ‘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’. (3.8)</td>
<td></td>
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<tr>
<td>We cannot emphasise enough the importance of the outcome of achieving stabilisation as highlighted in our submission and evidenced by the 2019 SMA Europe’s Community survey. In 2019, when 96.7% of 1,327 validated responses stated they would “consider it to be progress if there was a drug to stabilize their current clinical state.”</td>
<td></td>
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<tr>
<td>We note also, ‘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’ (3.9). We also noted a final comment at the committee hearing from one of the clinical experts who stated that their early experience of caring for people enrolled in the risdiplam EAMS was that she was noting an impact on swallowing and respiratory function. This was also raised by the adult patient expert in their evidence following a relatively short time (some months) taking risdiplam.</td>
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| 10 | **Cost effectiveness** |
| We were encouraged at the committee meeting to hear that the company and ERG, were both willing to discuss the challenges of the economic modelling and report back to NICE. Please see further comments in 11 – 15. |

| 11 | **Utility values – fine motor skills** |
| We draw attention to the following comment which is one we hear echoed in the SMA community many times ‘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’. (3.12) |
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We consider there is a need to adjust the modelling to reflect this in a way that incorporates a 'utility gain to reflect risdiplam’s potential benefits in fine motor skills' (3.12) and that it is, as the committee suggests one that reflects their observation that ‘The company’s utility gain for fine motor skills is acceptable but may be too low’. (3.16)

12 Utility values – other benefits
We agree with this comment:

‘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’. (3.17) We note that ‘The committee concluded that there could be some benefits that are not captured in the models’ (3.17). We hope to see adjustments to the modelling that reflect this.

13 Caregiver QALYs
We are concerned that this modelling resulted in, ‘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)’ (3.22) and hope that this will be addressed.

We are not health economists but suggest that modelling needs to reflect the differences that SMA UK’s experience suggests occur – see our summary below. (Please note this was a table 2 x 2 which is easier to follow but this template does not allow this)

<table>
<thead>
<tr>
<th>Caregiver Type 1</th>
<th>infant with no treatment - best supportive care</th>
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</thead>
<tbody>
<tr>
<td><strong>During infant’s lifetime – compared to treated infant</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Impact is more intense but for shorter period</strong></td>
<td></td>
</tr>
<tr>
<td>• Night and day care 24/7 – very intense and increasing – ongoing chronic care and acute issue</td>
<td></td>
</tr>
<tr>
<td>• Frequent hospital admissions – disruption to family life / work / siblings</td>
<td></td>
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<tr>
<td>• High stress and depression – no hope</td>
<td></td>
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<tr>
<td>• Lack of sleep and fatigue</td>
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<tr>
<td>• Lack of social contact</td>
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<tr>
<td>• Guilt – genetic inheritance</td>
<td></td>
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<tr>
<td>• Intense use of equipment at home</td>
<td></td>
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<tr>
<td>• Marital stress</td>
<td></td>
</tr>
<tr>
<td>• Impact on other siblings</td>
<td></td>
</tr>
<tr>
<td>• Loss of work – invariably one carer at least - financial impact</td>
<td></td>
</tr>
<tr>
<td>• High impact on extended family – need for their support and of friends and family</td>
<td></td>
</tr>
<tr>
<td><strong>After death– compared to treated infant</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Impact may be similar</strong></td>
<td></td>
</tr>
<tr>
<td>• Grief/ Depression / ongoing mental health impact – on carers and siblings</td>
<td></td>
</tr>
<tr>
<td>• Not infrequent marital / family breakdown</td>
<td></td>
</tr>
<tr>
<td>• Return to work /social life challenges</td>
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</table>

We note also that as clinical evidence suggests the earlier the treatment, the more positive the outcome, the assumption that treatment leads to care equivalent to Type 2 may be
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incorrect and caregiver impact may potentially be reduced further than outlined below.

<table>
<thead>
<tr>
<th>Caregiver Type 1 – <strong>Infant with treatment</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Based on assumptions that treatment is given early, infant responds well and moves to at least Type 2 / 3 care needs</td>
</tr>
<tr>
<td>➢ During infant’s lifetime - compared to non-treated (best supportive care)</td>
</tr>
<tr>
<td>Impact drops for some aspects but increases for others and new pressures emerge over time</td>
</tr>
</tbody>
</table>

**Decreases:**
- Night and day care hours – chronic needs decrease, acute episodes become less frequent
- Hospital admissions
- Hope decreases stress and depression
- Lack of sleep and fatigue - improves
- Lack of social contact – may improve
- Guilt – genetic inheritance – may be less as able to address this better via treatment

**Increases**
- Equipment and adaptation needs

**Not known:**
- Marital stress may continue due to sustaining care
- Impact on other siblings may continue due to sustaining care
- Loss of work – may continue until FT education is possible - financial impact

**After death**
**Impact may be similar**
- As family has been able to do all possible for their child during their lifetime this may help with feelings of guilt and depression **but**
- Other impacts of grief and loss remain for all affected

### 14 Stopping rules

We note this comment, ‘**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’.** (3.11)

‘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’ (3.11)

We suggest that these comments were made prior to work following the NICE nusinersen access for those who have SMA Type 3 decision, that led to a revision of these stopping rules. These new measures have been agreed by clinicians and patient groups. They now reflect the desired outcome of stabilisation and greater flexibility in terms of the use of scales and measurements that will reflect this and that recognise the importance of stabilisation of fine motor skills. There is a lay summary here: [https://smauk.org.uk/blog/treatments-research/how-scales-and-measurements-will-work-now-for-englands-maa-for-nusinersen](https://smauk.org.uk/blog/treatments-research/how-scales-and-measurements-will-work-now-for-englands-maa-for-nusinersen)
We acknowledge the limitations of scales that are insufficiently sensitive to capture subtle changes and that currently the all-important Patient Reported Outcome Measures (PROMS) are not collected. We suggest that this information is important for any future decisions and to assist with ascertaining which drugs work better for which groups. We are aware that this does present extra work and time for clinicians, in particular physiotherapists, and can be onerous for families / adults but imagine that they would all welcome the opportunity to add to the pool of knowledge about treatment efficacy. If measurements and stopping rules can operate without NICE / NHSE’s involvement but as part of clinical research funded via other routes, we would be in favour of this possibility.

15 Price
We hope that every effort is being made by the company and NHSE’s commercial arm to reach an agreed price that will allow this treatment to be recommended.

16 Are the recommendations sound and a suitable basis for guidance to the NHS?
Until such time as the economic modelling issues and costs have been addressed, we don’t consider the ‘no’ to NHS funding recommendation to be a sound and a suitable basis for guidance to the NHS.

The consultation paper notes ‘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.’ (3.21) The committee assures us that ‘The decision making takes into account the rarity and severity of the disease’ (3.21)

We remain concerned by the constraints of the STA system. We point out that nusinersen treatment was recommended following considerable work on the economic modelling and costs and that this was within the STA framework. We suggest that the clinical and real-world evidence of effectiveness for risdiplam heard by the committee is as robust as possible for any new treatment for a rare condition and note its innovative nature. We remind everyone involved in this appraisal, that for people who live with this progressive condition, every day counts and that their lives could be changed significantly and positively by this treatment. We would therefore expect work on the economic modelling and price to conclude swiftly and positively. We would expect NICE to enable any flexibility the STA process allowed for nusinersen to be enacted for risdiplam, resulting in a positive recommendation.

17 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

‘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’ (3.2) We hope that this decision making included that this is a home delivered option which acts in its favour in terms of enabling equality of access to disabled people. Many face significant challenges having to travel for treatment. During the pandemic many have had to shield and the prospect of travel, hospital visits for care and treatment and exposure to possible infection has been out of the question. Additionally, the option of nusinersen is not clinically safe / possible for many and they currently have no treatment options. We suggest these factors mean that risdiplam should be given special
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<thead>
<tr>
<th>Consideration.</th>
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Insert extra rows as needed

**Checklist for submitting comments**

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under ‘commercial in confidence’ in turquoise and all information submitted under ‘academic in confidence’ in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: ‘academic / commercial in confidence information removed’. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

**Note:** We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.