Technology Guidance

Nusinersen and risdiplam

for treating spinal muscular atrophy

Technology Guidance from the MOH Drug Advisory Committee

Guidance Recommendations

The Ministry of Health's Drug Advisory Committee has recommended:

- ✓ Risdiplam 0.75 mg/mL powder for oral solution for treating:
  - Symptomatic Type 1, 2 or 3 spinal muscular atrophy (SMA) in patients who are/were 18 years of age or under at the time of initial treatment with risdiplam or nusinersen;
  - Symptomatic Type 1, 2 or 3 SMA in patients aged 19 years or above who had not initiated treatment with risdiplam or nusinersen prior to 19 years of age despite onset of signs/symptoms of SMA;
  - Pre-symptomatic SMA in patients who are/were under 3 years of age at the time of initial treatment with risdiplam or nusinersen; and
  - SMA in patients who have experienced a regression in a developmental state despite treatment with gene therapy.

Funding status

Risdiplam 0.75 mg/mL powder for oral solution is recommended for inclusion on the Medication Assistance Fund (MAF) for the abovementioned indications from 1 August 2024.

Risdiplam should be used in line with the additional clinical criteria listed in the Annex.

MAF assistance **does not** apply to nusinersen for treating SMA.

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Factors considered to inform the recommendations for funding

Technology evaluation

1.1. At the March 2024 meeting, the MOH Drug Advisory Committee ("the Committee") considered the evidence presented for the technology evaluation of nusinersen and risdiplam for treating spinal muscular atrophy (SMA). The Agency for Care Effectiveness (ACE) conducted the evaluation in consultation with clinical experts from public healthcare institutions. Published clinical and economic evidence for nusinersen and risdiplam was considered in line with their registered indications.

1.2. The evidence was used to inform the Committee's deliberations around four core decision-making criteria:

- Clinical need of patients and nature of the condition;
- Clinical effectiveness and safety of the technology;
- Cost-effectiveness (value for money) – the incremental benefit and cost of the technology compared to existing alternatives; and
- Estimated annual technology cost and the number of patients likely to benefit from the technology.

1.3. Additional factors, including social and value judgments, may also inform the Committee's funding considerations.

Clinical need

2.1. SMA is a rare neuromuscular disorder that causes muscle weakness and wasting, leading to symptoms such as breathing difficulties and loss of motor function. SMA is caused by mutations or deletions in the survival motor neuron 1 (SMN1) gene, resulting in a deficiency of the SMN protein that is needed for normal neuron function. The nearby SMN2 gene also produces a small amount of the SMN protein. Patients with fewer copies of the SMN2 gene and symptom onset at a younger age typically have more severe SMA disease.

2.2. In Singapore, 40 - 60 patients have been diagnosed with SMA. Additionally, about 3 babies are born each year with SMA. There are currently 3 SMA treatments approved by the Health Sciences Authority (HSA). They comprise 2 drugs (nusinersen and risdiplam) intended for long-term use and a gene therapy (onasemnogene abeparvovec) which is a one-time treatment. Prior to the availability of these treatments, patients with SMA received best supportive care (BSC) such as physiotherapy, respiratory and orthopaedic care, and nutritional support.

2.3. The Committee acknowledged the clinical need to consider SMA treatments for funding, to improve treatment affordability and ensure appropriate patient care. In the current evaluation, nusinersen and risdiplam have been considered for inclusion on the MOH List of Subsidised Drugs. Onasemnogene abeparvovec will be reviewed in a subsequent evaluation for funding under a different financing framework.

2.4. Based on local expert input and overseas reimbursement criteria, the Committee noted the clinical need for nusinersen and risdiplam was in the following populations:

- Children with symptomatic Type 1, 2 or 3 SMA;
- Adults with symptomatic Type 1, 2 or 3 SMA;
- Children with pre-symptomatic SMA; and
- Patients with SMA who have experienced a regression in a developmental state despite treatment with gene therapy.

2.5. The Committee heard that Type 1 SMA is a severe form of the condition, with symptoms appearing within the first 6 months of life. Based on natural history, most affected individuals cannot control their head movement or sit unassisted. They may also have breathing and swallowing difficulties. Many do not survive beyond 2 years of age due to respiratory failure.

2.6. In Type 2 SMA, symptoms appear between 6 and 18 months of age. Affected individuals can sit without support but cannot stand or walk unaided. They may also have respiratory muscle weakness that can be life-threatening. The lifespan of these individuals varies, but many live into their 20s or 30s.

2.7. In Type 3 SMA, symptoms appear between 1.5 and 18 years of age. Most individuals can walk unaided, but some may require wheelchair assistance as motor function declines over time. Individuals with Type 3 SMA generally have a normal life expectancy.

2.8. Locally, there are adults with SMA who have not yet started on an approved treatment despite an onset of signs/symptoms before the age of 19 years. The Committee noted that this population would reduce over time if more patients can access treatment during childhood.

2.9. Individuals with a genetic diagnosis of SMA but who have not yet displayed signs/symptoms are considered to have pre-symptomatic SMA. According to clinical experts, early treatment in children during the pre-symptomatic phase may lead to better clinical outcomes, compared with treatment initiation in the symptomatic phase where the disease is more advanced.

2.10. For children who have received gene therapy for SMA, the Committee considered that the long-term durability of the treatment effect remains uncertain. Hence, the Committee noted a clinical need for a subsidised drug treatment for patients who have experienced a regression in a developmental state despite gene therapy.

Clinical effectiveness and safety

3.1. The Committee reviewed the available clinical evidence for nusinersen and risdiplam in children and adults with SMA. This included evidence from clinical trials, indirect treatment comparisons (ITCs), observational studies and overseas registry data.

3.2. Children with symptomatic Type 1, 2 or 3 SMA
For children with Type 1 SMA, the Committee reviewed clinical evidence for nusinersen and risdiplam from the ENDEAR and FIREFISH trials, respectively. For children with Type 2 or 3 SMA, they reviewed the CHERISH trial (nusinersen) and SUNFISH Part 2 trial (risdiplam). All the trials excluded patients who had received a gene therapy for SMA.

3.3. ENDEAR was a 13-month randomised controlled trial (RCT) that compared nusinersen with sham control in 121 children with infantile-onset (consistent with Type 1) SMA. The children were aged 7 months or younger at screening. Compared with the control group at the final analysis, more children treated with nusinersen remained alive (84% vs 61%) or were alive without the use of permanent assisted ventilation (61% vs 32%). The proportion of children who had a motor-milestone response was 51% in the nusinersen group versus 0% in the control group. In the open-label extension study, patients treated with nusinersen showed improvement in motor function.

3.4. FIREFISH was a single-arm trial for risdiplam in children with Type 1 SMA. At enrolment, the children were aged 7 months or younger. Among 58 children who received the therapeutic dose of risdiplam, 91% remained alive and 84% were alive without the use of permanent ventilation after 36 months of treatment. The children also maintained or continued to improve in measures of motor function over the 36 months.

3.5. CHERISH was an RCT that compared nusinersen with sham control in 126 children with later-onset SMA, who were deemed most likely to develop Type 2 or 3 SMA. The children were aged between 2 and 9 years at screening. At 15 months of treatment, the nusinersen group showed an improvement in motor function compared with the control group, as assessed by the Hammersmith Functional Motor Scale - Expanded (HFMSE) score. In the open-label extension study, patients treated with nusinersen showed stabilisation or improvement in motor function.

3.6. SUNFISH Part 2 was an RCT that compared risdiplam with placebo in 180 patients with Type 2 or 3 SMA. The enrolled population comprised 158 children (aged 2 to 17 years) and 22 adults (aged 18 to 25 years). At 12 months of treatment, the risdiplam group showed an improvement on the Motor Function Measure-32 (MFM32) scale compared with the placebo group. Long-term follow-up results showed that improvements in motor function scores were maintained with risdiplam treatment.

3.7. Based on the available evidence, the Committee agreed that treatment with either nusinersen or risdiplam provided meaningful clinical benefit in children with symptomatic Type 1, 2 or 3 SMA. In the absence of head-to-head trials between the 2 drugs, the Committee considered the results of ITCs that were reviewed by CADTH (Canada) and PBAC (Australia). While acknowledging the uncertainty associated with the ITCs, the Committee noted that nusinersen and risdiplam were likely to be comparable in clinical effectiveness, in line with local expert opinion.

3.8. In terms of safety, the Committee considered that nusinersen and risdiplam had different safety profiles given their different routes of administration. Nusinersen is administered via intrathecal injection, while risdiplam is given as an oral solution.

3.9. Adults with symptomatic Type 1, 2 or 3 SMA

The Committee noted that no comparative clinical trial has been conducted for nusinersen in adults with SMA. However, observational studies, overseas SMA registry data, and natural history studies in adults with Type 2 or 3 SMA suggested that nusinersen was more effective than BSC in stabilising or improving motor function, although the magnitude of benefit was uncertain.

3.10. For risdiplam, the Committee reviewed evidence from the SUNFISH Part 2 trial, which included an exploratory subgroup analysis of 22 adults (aged 18 to 25 years) who had Type 2 or 3 SMA. Results at 12 months of treatment suggested that motor function was generally stabilised in adults treated with risdiplam.

3.11. Overall, the Committee noted there was limited evidence on the use of either nusinersen or risdiplam in adults with Type 1, 2 or 3 SMA who had not initiated treatment before the age of 19 years. However, they considered that the treatments would likely provide clinical benefit over BSC for some adults with SMA, given the efficacy demonstrated in children. The Committee also acknowledged that providing a subsidised treatment option for adults will ensure equity of access to treatment across all ages.

3.12. To manage the uncertainty around the magnitude of benefit with nusinersen and risdiplam in the adult population, the Committee agreed that the drugs should be used in line with additional clinical criteria, to assess patients' response to treatment and to ensure that only patients who show a clinically meaningful response may continue subsidised treatment beyond 2 years.

3.13. Children with pre-symptomatic SMA

For children with pre-symptomatic SMA, the Committee reviewed clinical evidence from the NURTURE and RAINBOWFISH trials, involving treatment with nusinersen and risdiplam, respectively. Both were single-arm trials that included children up to 6 weeks of age at the time of first treatment dose, and who had not received a gene therapy for SMA.

3.14. The NURTURE trial for nusinersen enrolled 25 children who had 2 or 3 copies of the SMN2 gene and were deemed most likely to develop Type 1 or 2 SMA. After approximately 5 years of treatment, all 25 children were alive and none required permanent ventilation or had regression of motor function. Most had also achieved motor milestones within the normal developmental timeframe for healthy children.

3.15. The RAINBOWFISH trial for risdiplam enrolled 26 children who had 2 or more copies of the SMN2 gene. Based on an interim analysis of 7 children who had received risdiplam for at least 12 months, all were alive without requiring permanent ventilation. Most had also achieved motor milestones within the expected timeframe for healthy children.

3.16. Overall, the Committee agreed the evidence showed that children with pre-symptomatic SMA who received nusinersen or risdiplam had meaningful improvements in clinical outcomes, which were in contrast with the natural history of untreated SMA. The Committee also noted the results of an ITC reviewed by PBAC, which suggested an incremental clinical benefit when nusinersen was initiated in the pre-symptomatic phase compared with the symptomatic phase of SMA.

3.17. Patients with SMA who have experienced a regression in a developmental state despite treatment with gene therapy
The Committee noted the lack of clinical evidence on the use of nusinersen or risdiplam as a subsequent treatment in patients who have experienced a regression in a developmental state despite gene therapy. However, they acknowledged that in overseas jurisdictions, nusinersen and risdiplam are reimbursed for this population.

3.18. The Committee agreed that nusinersen and risdiplam may be considered for funding if they were used in line with additional criteria to manage the clinical uncertainty. The criteria would define the childhood development states and ensure that only patients who have a documented regression after gene therapy may receive subsidised drug treatment.

Cost effectiveness

4.1. The Committee reviewed the economic evaluations from overseas HTA agencies, which reported high incremental cost-effectiveness ratios (ICERs) when nusinersen or risdiplam was compared with BSC in patients with SMA. The Committee also noted the agencies' assessments that the ICERs were uncertain and difficult to interpret due to various factors such as limited evidence to substantiate longer-term benefits and limitations with the model structure. Hence, the agencies had used a combination of approaches to address the uncertainty in the evidence and improve the cost effectiveness of the treatments. These approaches included price reductions, cost-minimisation, risk-sharing arrangements and/or clinical criteria for starting and stopping treatment.

4.2. The companies of nusinersen and risdiplam were invited to submit pricing proposals for their products for funding consideration in Singapore. The Committee agreed that a cost-minimisation approach was appropriate to identify the drug with lower treatment cost for funding consideration, given that nusinersen and risdiplam are likely to be comparable in clinical effectiveness with different safety profiles. Using the same equi-effective doses as published by the PBAC, risdiplam 5 mg daily and nusinersen 12 mg per administration every 4 months, the cost-minimisation analysis showed that risdiplam had a lower treatment cost than nusinersen at the companies' proposed prices.

4.3. When compared with prices in overseas reference jurisdictions, the Committee considered risdiplam likely to represent an acceptable use of healthcare resources for treating SMA in the 4 populations under review. The Committee also acknowledged that the company's pricing proposal for risdiplam was adequate to manage the uncertainty of the overall budget impact.

Estimated annual technology cost

5.1. The Committee noted that the cost impact to the public healthcare system was estimated to be between SG$5 million and SG$10 million per year, in the first 5 years of listing risdiplam on the MOH List of Subsidised Drugs.

Recommendations

6.1. Given the high clinical need for an effective SMA treatment, the totality of clinical evidence, and that risdiplam is considered to be an acceptable use of healthcare resources, the Committee recommended risdiplam 0.75 mg/mL powder for oral solution be listed on the Medication Assistance Fund (MAF) for the treatment of:

- Symptomatic Type 1, 2 or 3 SMA in patients who are/were 18 years of age or under at the time of initial treatment with risdiplam or nusinersen;
- Symptomatic Type 1, 2 or 3 SMA in patients aged 19 years or above who had not initiated treatment with risdiplam or nusinersen prior to 19 years of age despite onset of signs/symptoms of SMA;
- Pre-symptomatic SMA in patients who are/were under 3 years of age at the time of initial treatment with risdiplam or nusinersen; and
- SMA in patients who have experienced a regression in a developmental state despite treatment with gene therapy.

6.2. The Committee also recommended risdiplam be used in line with additional clinical criteria (listed in the Annex) to govern appropriate use in local practice. The criteria were developed in consultation with local clinical experts and are consistent with overseas reimbursement criteria.

6.3. The Committee recommended not listing nusinersen on the MOH List of Subsidised Drugs due to unfavourable cost effectiveness compared with risdiplam at the proposed prices.

ANNEX

MAF clinical criteria for risdiplam

1) **Treatment of symptomatic Type 1, 2 or 3 spinal muscular atrophy (SMA) in patients who are/were 18 years of age or under at the time of initial treatment with risdiplam or nusinersen.**
   - Patient must be untreated with gene therapy; and
   - The condition must have genetic confirmation of 5q homozygous deletion of the SMN1 gene, or genetic confirmation of deletion of one copy of the SMN1 gene in addition to a pathogenic / likely pathogenic variant in the remaining copy of the SMN1 gene; and
   - The treatment must be given concomitantly with best supportive care for this condition in a multidisciplinary setting; and
   - The treatment must be ceased when invasive permanent assisted ventilation (i.e. ventilation via tracheostomy tube for ≥16 hours per day) is required in the absence of a potentially reversible cause while being treated with this drug; and
   - Patient must be treated by, or in consultation with, a specialist physician experienced in the diagnosis and management of SMA.

2) **Treatment of symptomatic Type 1, 2 or 3 spinal muscular atrophy (SMA) in patients aged 19 years or above who had not initiated treatment with risdiplam or nusinersen prior to 19 years of age despite onset of signs/symptoms of SMA.**
   - Patient must be untreated with gene therapy; and
   - The condition must have genetic confirmation of 5q homozygous deletion of the SMN1 gene, or genetic confirmation of deletion of one copy of the SMN1 gene in addition to a pathogenic / likely pathogenic variant in the remaining copy of the SMN1 gene; and
   - There must be confirmation that the patient's medical history is consistent with a diagnosis of SMA during childhood; and
   - The treatment must be given concomitantly with best supportive care for this condition in a multidisciplinary setting; and
   - The treatment must be ceased when invasive permanent assisted ventilation (i.e. ventilation via tracheostomy tube for ≥16 hours per day) is required in the absence of a potentially reversible cause while being treated with this drug; and
   - Patient must be treated by, or in consultation with, a specialist physician experienced in the diagnosis and management of SMA.

Undertake comprehensive assessments (i) at baseline before treatment initiation, and (ii) at least every 6 months after treatment initiation. Document these assessments in the patient's records.

- Comprehensive assessments, where practical, should encompass the patient's motor function as assessed using an instrument such as the Revised Upper Limb Module (RULM), Hammersmith Functional Motor Scale - Expanded (HFMSE), 6-minute walk test (6MWT), Motor Function Measure (MFM), Children's Hospital of Philadelphia Adult Test of Neuromuscular Disorders (CHOP ATEND), or Timed Up and Go Test (TUG); and the patient's quality of life as assessed using an instrument such as the SMA Health Index (SMA-HI) or SMA Functional Rating Scale (SMAFRS).

After a minimum treatment duration of 2 years,

- Comprehensive assessments involving the patient and the treating physician should establish agreement that treatment is continuing to produce a clinically meaningful response.
- A clinically meaningful response is present where an improvement, stabilisation or minimal decline in symptoms has occurred as a result of this drug treatment and where there is agreement between the treating physician and patient over what constitutes improvement, stabilisation, or minimal decline.
- Funding must cease if there is no agreement on whether a clinically meaningful response is present.
- Undertake re-assessments for a clinically meaningful response at least every 6 months.

3) Treatment of pre-symptomatic spinal muscular atrophy (SMA) in patients who are/were under 3 years of age at the time of initial treatment with risdiplam or nusinersen.

- Patient must be untreated with gene therapy; and
- The condition must have genetic confirmation that there are 3 or fewer copies of the SMN2 gene; and
- The condition must have genetic confirmation of 5q homozygous deletion of the SMN1 gene, or genetic confirmation of deletion of one copy of the SMN1 gene in addition to a pathogenic / likely pathogenic variant in the remaining copy of the SMN1 gene; and
- The treatment must be given concomitantly with best supportive care for this condition in a multidisciplinary setting; and
- The treatment must be ceased when invasive permanent assisted ventilation (i.e. ventilation via tracheostomy tube for ≥16 hours per day) is required in the absence of a potentially reversible cause while being treated with this drug; and
- Patient must be treated by, or in consultation with, a specialist physician experienced in the diagnosis and management of SMA.

4) Treatment of spinal muscular atrophy (SMA) in patients who have experienced a regression in a developmental state despite treatment with gene therapy.

- Patient must have experienced a regression in a developmental state listed below (see 'Definition') despite treatment with gene therapy, that is: (i) not due to an acute concomitant illness, (ii) not due to non-compliance to best supportive care, (iii) apparent for at least 3 months, and (iv) verified by another physician; and

- The condition must have genetic confirmation of 5q homozygous deletion of the SMN1 gene, or genetic confirmation of deletion of one copy of the SMN1 gene in addition to a pathogenic / likely pathogenic variant in the remaining copy of the SMN1 gene; and
- The treatment must be given concomitantly with best supportive care for this condition in a multidisciplinary setting; and
- The treatment must be ceased when invasive permanent assisted ventilation (i.e. ventilation via tracheostomy tube for ≥16 hours per day) is required in the absence of a potentially reversible cause while being treated with this drug; and
- Patient must be treated by, or in consultation with, a specialist physician experienced in the diagnosis and management of SMA.

Definition:
Various childhood developmental states (1 to 9) are listed below, some followed by further observations (a up to d). Where at least one developmental state/observation is no longer present, that developmental state has regressed.

0. Absence of developmental states (1 to 9) listed below:
1. Rolls from side to side on back.
2. Child holds head erect for at least 3 seconds unsupported.
3. Sitting, but with assistance.
4. Sitting without assistance:
   (a) Child sits up straight with the head erect for at least 10 seconds;
   (b) Child does not use arms or hands to balance body or support position.
5. Hands and knees crawling:
   (a) Child alternately moves forward or backwards on hands and knees;
   (b) The stomach does not touch the supporting surface;
   (c) There are continuous and consecutive movements at least 3 in a row.
6. Standing with assistance:
   (a) Child stands in upright position on both feet, holding onto a stable object (e.g. furniture) with both hands and without leaning on object;
   (b) The body does not touch the stable object, and the legs support most of the body weight;
   (c) Child thus stands with assistance for at least 10 seconds.
7. Standing alone:
   (a) Child stands in upright position on both feet (not on the toes) with the back straight;
   (b) The leg supports 100% of the child's weight;
   (c) There is no contact with a person or object;
   (d) Child stands alone for at least 10 seconds.
8. Walking with assistance:
   (a) Child is in an upright position with the back straight;
   (b) Child makes sideways or forced steps by holding onto a stable object (e.g. furniture) with 1 or both hands;
   (c) One leg moves forward while the other supports part of the body weight;
   (d) Child takes at least 5 steps in this manner.

9. Walking alone:
   (a) Child takes at least 5 steps independently in upright position with the back straight;
   (b) One leg moves forward while the other supports most of the body weight;
   (c) There is no contact with a person or object.

Confirm which developmental state has regressed by: (i) stating the overall developmental state (1 - 9) the patient was in at the time of gene therapy, or, the best developmental state achieved since gene therapy, and (ii) stating the patient's current overall developmental state [i.e. a number that is lower than stated in (i)]. Document these in the patient's medical records.