Risdiplam

REJECTED

The Expert Committee, after evaluation, declines to list the medicine proposed in the application.
The Model List of Essential Medicines reports reasons that Committee Members have identified for denying listing.

Section: 5. Medicines for neurological disorders

EMLc | ATC codes: M09AX10

Indication	Spinal muscular atrophy ICD11 code: 8B61.Z
INN	Risdiplam
Medicine type	Chemical agent
List type	Core
Formulations	**Oral > Liquid:** 0.75 mg per mL powder for oral liquid **Oral > Solid > dispersible tablet:** 5 mg
EML status history	Application rejected in 2023 (TRS 1049) Application rejected in 2025 (TRS 1064)
Sex	All
Age	Also recommended for children
Therapeutic alternatives	The recommendation is for this specific medicine
Patent information	Main patent is active in several jurisdictions. For more information on specific patents and license status for developing countries visit www.MedsPal.org Read more about patents.
Wikipedia	Risdiplam
DrugBank	Risdiplam

Expert Committee recommendation

The Expert Committee again acknowledged the considerable morbidity and mortality associated with spinal muscular atrophy and the public health relevance of effective treatments. Considering SMA as a rare disease, the Committee reaffirmed the importance of equity, and that the rarity of a condition must not preclude medicines for its treatment from being included on the Model Lists if they meet essential medicines selection criteria. There are currently no treatments for SMA included on the Model Lists. The Committee noted the evidence presented in the application from the FIREFISH and SUNFISH trials in symptomatic patients with SMA was the same as that presented in the 2023 application, with no new data reported. As in 2023, the Committee noted that the available evidence in this population remains limited and uncertain. In terms of benefits, the Committee again noted that greater improvements in motor function were reported in younger children (<5 years) than in older children, adolescents and adults. The Committee considered that risdiplam shows the greatest efficacy in the treatment of presymptomatic infants with SMA. The Committee considered new evidence from the RAINBOWFISH trial in this population, presenting results following 24 months of treatment. Evidence in the previous application presented results following 12 months of treatment. The Committee noted the promising 24-month results which indicated favourable outcomes for sitting without support, standing alone, and walking alone among treated infants, with most achieving age-appropriate motor milestones. Additionally, all treated infants were reported to maintain bulbar function, and none required permanent ventilation. However, to date, these data have been reported only

in a conference presentation and have not yet been evaluated by the clinical and scientific community and published in a peer-reviewed journal. As such, the internal and external validity of the results could not be fully assessed by the Expert Committee due to limited available information. Based on these considerations, the Expert Committee did not recommend the inclusion of risdiplam on the EML and EMLc at this time. However, the Committee requested that an application for risdiplam, focusing on a clearly defined population of presymptomatic infants with SMA, presenting updated, published results of the RAINBOWFISH trial be submitted for consideration by the 2027 Expert Committee. The Committee considered that if the preliminary results of the 24-month follow-up of the RAINBOWFISH trial are confirmed, if the risk of bias associated with the trial is low, and if no evidence emerges against use of risdiplam in this population (e.g. serious safety concerns), then a positive recommendation to include risdiplam on the EMLc could be possible in 2027. Considering the current very high price of risdiplam, and reports of patent challenges and compulsory license cases currently ongoing in India which have strong potential to result in the availability of generics and lower prices, the Committee requested the next application provide an updated overview of price and availability of risdiplam across different settings. Recognizing also the importance of newborn screening to identify infants with presymptomatic SMA most likely to benefit from risdiplam treatment, information on the availability and implementation of newborn screening for SMA should also be included in the next application.

Background

There are currently no treatments for SMA included on the EML and EMLc. Risdiplam was previously considered for inclusion on the EML and EMLc for the treatment SMA in paediatric and adult patients in 2023 (1). The 2023 Expert Committee acknowledged that SMA was associated with considerable morbidity and mortality in affected children and adults. While it has a relatively low incidence in the general population, disease clusters are possible, particularly in families with increased prevalence of consanguinity. The Committee reaffirmed that the low incidence of a disease is not a factor on its own that precludes the inclusion of medicines on the Model Lists, and highlighted that essential medicines for rare diseases had been included since the first Model List was published in 1977 (e.g. blood coagulation factors for haemophilia and antirabies hyperimmune serum (later equine rabies immunoglobulin)). The Committee noted the current availability of three treatments for SMA: one small molecule (risdiplam); one antisense oligonucleotide (nusinersen); and one gene therapy (onasemnogene abeparvovec). These treatments share some characteristics: they are associated with potentially important clinical benefits which appear to be greatest with the early introduction of treatment in presymptomatic infants who carry the survival motor neuron 1 gene (SMN1) gene mutation responsible for SMA, and in symptomatic patients with recent onset of symptoms; and they all have a high price. Between risdiplam and nusinersen, the Committee noted the greater feasibility of risdiplam over nusinersen. Nusinersen requires administration by intrathecal injection every 4 months which must be done in hospital by trained health professionals, while risdiplam is administered orally. Nusinersen also has adverse effects such as headache, vomiting, back pain and risk of infections. The Committee noted that the body of evidence for efficacy and safety of risdiplam in SMA was still limited, with only a small number of patients exposed to long-term treatment. The Committee noted that most patients had a disease duration of at least 3 months when they were enrolled in the clinical trials. About 50% of children treated with risdiplam showed improvement in motor function (e.g. sitting without support for ≥ 5 seconds) at 24 months, and more children achieved motor milestones with prolonged treatment. While risdiplam is likely associated with longer survival without the requirement for permanent mechanical ventilation, based on the available data, no participants could stand or walk alone when risdiplam had been given after disease onset. The Committee noted that based on the available evidence in patients with symptomatic disease, improvements in motor function were observed in younger children (< 5 years) but that these improvements became increasingly less noticeable in older children, adolescents and adults. Treatment-related adverse effects were generally mild. Overall, the Committee considered that the magnitude and long-term duration of benefits and potential harms of risdiplam were still uncertain. The Committee noted that newborn screening for SMA had been introduced into routine screening panels in some high-income countries in recent years. However, the effectiveness of such screening programmes in identifying potential patients in a presymptomatic stage of the disease had not yet been assessed. The Committee also noted the preliminary results of ongoing clinical trials of risdiplam in presymptomatic infants

up to 6 weeks of age. As risdiplam is likely to be associated with larger benefits when treatment is started before symptom onset, the Committee considered that it would be important to study its long-term effectiveness in those settings where routine newborn screening programmes for SMA are implemented. The Committee advised that data on SMA screening programmes and use of risdiplam in presymptomatic infants should be reviewed as they become available, as well as the outcomes of longer-term clinical trials for risdiplam in older, less severely affected, symptomatic patients. The Committee noted the current high price of risdiplam and that reimbursement decisions in some high-income countries have been made subject to managed entry arrangements or price reduction, and that generic versions of risdiplam were not currently available. The Committee noted that a request made by Knowledge Ecology International for a voluntary licence to manufacture and sell a generic version of risdiplam had not been granted by the patent holder. Nevertheless, the Committee considered that risdiplam could be flagged to the Medicines Patent Pool as a potential candidate for negotiating public health-oriented licences to facilitate affordable access in low- and middle-income countries. Based on these considerations, the 2023 Expert Committee did not recommend listing risdiplam.

Public health relevance

SMA is an autosomal recessive genetic disease characterized by the degeneration of lower motor neurons in the spinal cord. It is caused by deletion or mutation of the SMN1 gene, which codes for the survival motor neuron protein, a protein critical for motor neuron survival. Symptoms include skeletal muscle atrophy, progressive generalized weakness and respiratory failure, potentially leading to early death (2, 3). The disease has been divided into five types, based on age at symptom onset and maximum motor function achieved in untreated patients (4). Type 0 is a rare and severe type of SMA with symptoms beginning before birth. At birth, the infant presents with severe weakness and difficulty in breathing and feeding. Type 1 is the most common form of the disease and symptom onset is before 6 months of age, with children presenting with severe muscle weakness and trouble breathing and swallowing. Type 2 is noticed between 6 and 18 months of age and children with this type can usually sit without support but are unable to stand or walk without help. Type 3 shows symptoms after 18 months of age and children normally can walk independently but have difficulty doing so, and they may have trouble running, rising from a chair or climbing stairs. Type 4 develops after 18 years of age and symptoms include mild to moderate leg muscle weakness (5). The incidence of SMA has been estimated at around 1 in 10 000 live births, with a prevalence of about 1–2 per 100 000 people. Since SMA is a rare condition, studies of its prevalence and incidence are challenging, and the numbers vary across populations (6). SMA is the most common monogenic cause of death among infants (3). For SMA type 1, in the absence of treatment, the mortality rate is greater than 90% by 2 years of age (4). Due to decreasing physical abilities, motor functions and potential death caused by the disease, patients and families often experience a substantial psychological and emotional burden (7). Apart from risdiplam, two other medicines are available for the treatment of SMA: nusinersen and onasemnogene abeparvovec. Nusinersen is an antisense oligonucleotide administered via intrathecal injection, which requires a hospital setting. It is not suitable for patients with spinal deformities, scoliosis or previous scoliosis surgery, which are common in patients with the disease. Onasemnogene abeparvovec is a gene therapy administered through a one-time intravenous infusion, also requiring a hospital setting. In contrast, risdiplam is an oral medicine that can be administered at home and does not require hospitalization. SMA patients have at least one copy of the survival motor neuron 2 gene (SMN2), which produces an unstable form of survival motor neuron protein. Both risdiplam and nusinersen target this gene, while onasemnogene abeparvovec acts on gene SMN1. All three medicines are considered to have a high cost (8). None of these therapies is a cure for SMA.

Benefits

Risdiplam has been evaluated in three clinical trials: RAINBOWFISH, FIREFISH and SUNFISH. RAINBOWFISH is a pharmaceutical-company-funded, open-label, single-arm, multicentre clinical study of the efficacy, safety, pharmacokinetics and pharmacodynamics of risdiplam in presymptomatic infants aged from birth to 6 weeks who have been genetically diagnosed with SMA with 2, 3 or ≥ 4 copies of SMN2. A total of 26 participants were enrolled in the intention-to-treat population, aged between 16 and 41 days. Median age at first dose was 25 days. Eligibility criteria included the absence of the need for invasive ventilation, tracheostomy or awake non-invasive ventilation,

and absence of concomitant or previous administration of other medicines targeting SMN2 or gene therapy. The primary efficacy endpoint was the proportion of the primary efficacy population (infants with 2 SMN2 copies and compound muscle action potential amplitudes ≥ 1.5 mV at baseline, n = 5) able to sit without support for ≥ 5 seconds at 12 months. Secondary endpoints (all participants) included: percentage of participants who develop clinically manifested SMA; time to permanent ventilation and/or death; percentage of participants who are alive without permanent ventilation; percentage of participants who achieve motor milestones; motor function measures; growth measures; nutritional status; and additional clinical parameters. Updated results since the data presented in the previous application have been reported in conference proceedings after 12 and 24 months of treatment. Two-year data from RAINBOWFISH were presented at the World Muscle Society Annual Congress in October 2024 (9). A total of 23 infants completed 24 months of treatment. At 24 months, all infants with 2 SMN2 copies (n = 5) could sit without support, 3/5 (60%) could stand alone and 3/5 (60%) were able to walk independently. Among infants with 3 SMN2 copies (n = 13), 12/13 (92%) could sit without support for ≥ 30 seconds, and all could stand alone and walk independently. Among infants with ≥ 4 SMN2 copies (n = 5), 4/5 (80%) could sit without support for ≥ 30 seconds and all could stand alone and walk independently. Most infants with 3 or ≥ 4 SMN2 copies were able to achieve age-appropriate motor milestones within windows of achievement established by the WHO Multicentre Growth Reference Study Group (10). Clinically manifested SMA was reported in 6/26 (23%) infants, all of whom had 2 SMN2 copies. All infants who completed 24 months of treatment were able to speak and maintained swallowing and feeding abilities. None required permanent ventilation. After 24 months of treatment, cognitive skills typical of normal child development were reported. FIREFISH was a company-sponsored, open-label, multicentre study to investigate safety, tolerability, efficacy, pharmacokinetics and pharmacodynamics of risdiplam in infants with symptomatic type 1 SMA and age between 1 and 7 months. The study was divided in two parts, an exploratory dose-finding part (part 1) and a confirmatory part (part 2) to investigate the treatment with the dose selected in the first part. In FIREFISH part 1, 21 participants were enrolled (11). Eligibility criteria included clinical diagnosis of type 1 SMA and genetic diagnostic confirmation of 5q-SMA. Patients who had previously received nusinersen and/or who required invasive ventilation or tracheostomy were excluded. The age range of the participants at symptom onset was 28 days to 3 months. The median age at enrolment was 6.7 months. At month 12, 7/21 (33%) participants, all in the high-dose cohort that was selected for part 2 (0.2 mg/kg per day), were able to sit without support for ≥ 5 seconds. In FIREFISH part 2, 41 participants aged between 1 and 7 months were enrolled (12, 13). The eligibility criteria were the same as in the first part of the study. The median age at enrolment was 5.3 months. At baseline, no participants were able to sit without support, the median Children's Hospital of Philadelphia Infant Test for Neuromuscular Disease (CHOP-INTEND) score was 22.0 and the median Hammersmith Infant Neurological Examination Module 2 (HINE-2) score was 1.0. After 12 months of treatment, 12/41 (29%) participants were able to sit without support for ≥ 5 seconds, 23/41 (56%) participants had a CHOP-INTED score of 40 or higher and 37/41 (90%) had an increase of at least 4 points from baseline in their CHOP-INTEND score. At month 12, 32/41 (78%) participants were classified as having a HINE-2 motor-milestone response. After 24 months of treatment, 18/41 (44%) participants were able to sit without support for at least 30 seconds. No participants could stand alone or walk alone after 24 months. SUNFISH was a company-funded, multicentre, randomized, double-blind, placebo-controlled, phase II/III study to investigate the safety, tolerability, efficacy, pharmacokinetics and pharmacodynamics of risdiplam in non-ambulant adult and paediatric participants with type 2 and type 3 SMA. It was divided in two parts, an exploratory dose-finding part (part 1) for 12 weeks and then a confirmatory part (part 2) for 24 months. The eligibility criteria included a confirmed diagnosis of 5q-SMA, the absence of previous or concomitant use of nusinersen and other criteria. The age group eligible for study was between 2 and 25 years. SUNFISH part 1 enrolled 51 participants. The median age at screening was 7 years and 4/51 (8%) were aged ≥ 18 years (14). Most participants (73%) had type 2 SMA. The median age of symptom onset was 14 months. Participants achieved a mean increase of 2.7 points in the 32-item Motor Function Measure (MFM32) from baseline to month 24. Participants achieved a mean increase of 2.5 points in the Revised Upper Limb Module (RULM) score and an overall increase of 0.6 points in the Hammersmith Functional Motor Scale-Expanded (HFMSE) score. Greater improvements in motor function were observed in younger participants (2–11 years) than in older participants (12–25 years). SUNFISH part 2 enrolled 180 participants, 128 (71%) with type 2 SMA and 52 (29%) with type 3 (15). At screening, 68 (38%) were aged 12 years or older. Participants achieved a mean increase change from baseline to month 12 in MFM32 total score of

1.36 points in the risdiplam group. Mean change from baseline to month 12 in RULM total score was of 1.61 points. In HFMSE total score, mean change after 12 months was of 0.95 points. The greatest improvements in the scores were observed in the youngest patients. Comparisons of risdiplam with other medicines for SMA No direct comparison studies between risdiplam and the other treatments for SMA have been conducted. A 2024 study evaluated long-term comparative efficacy and safety of risdiplam and nusinersen in children with type 1 SMA using an indirect treatment comparison method and data from 58 children in FIREFISH and aggregate data from 81 children enrolled in the ENDEAR and SHINE clinical trials of nusinersen (16). The study was funded by the manufacturer of risdiplam The study reported that risdiplam was superior to nusinersen for overall survival (hazard ratio (HR) 0.22, 95% CI 0.04 to 0.47) and event-free survival (HR 0.19, 95% CI 0.07 to 0.35). Risdiplam treatment was also associated with greater likelihood of achieving HINE-2 motor milestones (HR 1.45, 95% CI 1.21 to 1.80) and achieving ≥ 4-point improvement on CHOP-INTEND (HR 2.86, 95% CI 2.18 to 4.48). A 2023 systematic review and meta-analysis of six randomized controlled trials (728 participants) evaluated the efficacy and safety of risdiplam and nusinersen in the treatment of SMA (17). The majority (5/6) of the trials included participants with types 2–4 SMA. No comparisons between treatments were made. The study concluded that both nusinersen and risdiplam were effective in the treatment of SMA, showing clinical improvement in motor function as measured by HFMSE and RULM, and were similar in terms of adverse effects when compared with placebo. A 2022 study conducted an indirect treatment comparison of risdiplam with nusinersen and onasemnogene abeparvovec in patients with SMA (18). The study evaluated Individual patient data from risdiplam trials in comparison with aggregated data from published studies of the other treatments. From indirect comparisons of risdiplam and nusinersen in patients with type 1 SMA, the study found improved survival and motor function favouring risdiplam. The authors were unable to draw conclusions on the comparisons of risdiplam and nusinersen in patients with type 2/3 SMA, and risdiplam and onasemnogene abeparvovec in Type 1 SMA due to substantial differences in study populations.

Harms

From 24-month results of the RAINBOWFISH trial, no treatment related adverse events leading to study withdrawal or treatment discontinuation were reported (9). In addition, no deaths or treatment-related serious adverse events were reported. The most commonly reported adverse events were teething (42%) and gastroenteritis (38%). Most adverse events were not considered to be treatment-related and resolved over time. In FIREFISH part 1, 202 adverse events were reported, including 24 serious adverse events (11). The most common adverse events were pyrexia (52%), upper respiratory tract infection (43%), cough (24%) and vomiting (24%). The most common serious adverse events were pneumonia (14%), viral respiratory tract infection (10%) and acute respiratory failure (10%). Four infants died of respiratory complications, mainly due to the neuromuscular respiratory failure caused by the disease. In FIREFISH part 2, at a clinical cut-off date of 12 November 2020, 359 adverse events were reported, including 28/41 (68%) infants with serious adverse events (12). The most frequently reported adverse events occurring in five or more participants were upper respiratory tract infection (54%), pneumonia (46%) and pyrexia (44%). Fatal events were reported in three infants, considered unrelated to treatment and secondary to SMA-related respiratory complications. In SUNFISH part 2, 789 adverse events in risdiplam-treated participants were reported, with 93% of participants experiencing at least one adverse event and 20% experiencing at least one serious adverse event (15). The most frequently reported adverse events were upper respiratory tract infection (32%), nasopharyngitis (26%), pyrexia (21%) and headache (20%). The most frequently reported serious adverse event was pneumonia (8%). Adverse events with an incidence of ≥ 5 percentage points higher in the risdiplam group than the placebo group were pyrexia, diarrhoea and rash. No fatal adverse events were reported.

Cost / cost effectiveness

All three medicines available for the treatment of SMA currently have a high cost. Risdiplam pricing varies considerably across countries, with list prices reported in the application ranging from 529 United States dollars (US$) per unit (60 mg/80 mL powder for oral liquid) in China to US$ 13 504 per unit in the United States of America. The application described health technology assessment performed by agencies in Australia (19), Brazil (20, 21), Canada (22), France (23), Ireland (24), Kingdom of the Netherlands (25), New Zealand (26), Portugal (27) and the

United Kingdom of Great Britain and Northern Ireland (28). In most countries, risdiplam was associated with very high incremental cost–effectiveness ratios generally considered not to be cost-effective. In countries where risdiplam has been recommended for reimbursement, most agencies have recommended reimbursement subject to conditions such as (confidential) price reductions, rebates or managed access arrangements. Many countries limit reimbursement to treatment of patients with SMA types 1, 2 and 3 only. Results from a modelled cost–effectiveness evaluation of risdiplam versus nusinersen in people with SMA type 1 in China was reported in abstract form in 2022 (29). The model evaluated 10-year costs and effectiveness from a Chinese health-care system perspective. Risdiplam-treated patients had higher life-year and quality-adjusted life year gains. Direct medical costs associated with risdiplam treatment were lower than those for nusinersen. The study therefore concluded that risdiplam was dominant over nusinersen in China. A similar cost–effectiveness analysis in France found risdiplam dominated nusinersen in patients with SMA types 1, 2 and 3 (30). A 2024 systematic review aggregated data from 20 economic studies evaluating the cost–effectiveness of risdiplam, nusinersen, onasemnogene abeparvovec and best supportive therapy in the treatment of SMA types 1 and 2. The analyses found that none of the treatments were cost-effective compared with best support therapy care (31). The application also highlighted budget impact analyses that have reported the possibility of risdiplam being a cost-saving intervention when compared with alternative treatments for SMA (32–33).

WHO guidelines

WHO guidelines for treatment of SMA are not available.

Availability

Risdiplam has market authorizations in more than 100 countries for the treatment of SMA in patients aged 2 months and older. Market approval has been filed in several other countries. In some of these countries, the label was extended to include patients younger than 2 months based on positive interim data from RAINBOWFISH. The United States Food and Drug Administration approval for a dispersible tablet formulation of risdiplam was announced in early 2025. Generic brands of risdiplam are not currently available. Roche and PTC Therapeutics have numerous patents covering the medicine in around 120 countries. The applicant has asked the manufacturer for a voluntary licence to produce and sell a generic version of risdiplam, however, these requests have been declined.

Other considerations

In about 33 countries, SMA is now tested at birth through routine newborn screening programmes that identify the disease (34). The testing for SMA varies by country context. In the next few years, this number is expected to increase steadily, especially in countries where medicines targeting the disease are available (35). The Department of Mental Health, Brain Health and Substance Use reviewed and provided comments on the application. It highlighted that the feasibility of implementation and use of risdiplam in low-resource settings remains a challenge in that genetically confirmed SMA requires capacity and resources to diagnose and treat. These include specialist health-care workers, laboratories with diagnostic capabilities and health-care systems with strong supportive services. However, oral administration of risdiplam is especially suited for resource-constrained settings and given its potential to slow, halt or, in many cases, reverse disease progression, caregiver burden is likely to decrease with administration of this medication. The WHO Department Maternal, Newborn, Child and Adolescent Health and Ageing supported the inclusion of risdiplam on the EMLc, highlighting that it is the only orally administered disease-modifying therapy currently available for SMA, and it may be the best choice in low- and middle-income countries.

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