

**PROPOSAL
FOR THE INCLUSION OF RISDIPLAM
IN THE WHO MODEL LIST OF ESSENTIAL MEDICINES FOR
THE TREATMENT OF SPINAL MUSCULAR ATROPHY**

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List of Tables

Table 1: Safety comparison risdiplam

Table 2: Cost comparison of current SMA treatments

Table 3: CADTH SMA cost comparison

Table 4: National phase filings for two Roche WIPO PCT risdiplam patent applications, as of November 14, 2022.

1. Summary statement of the proposal for inclusion, change or deletion.

Risdiplam is sold under the trade Evrysdi by F. Hoffmann-La Roche (hereafter Roche). It is indicated for the treatment of spinal muscular atrophy (SMA) in pediatric and adult patients and should be added to the Essential Medicines List (EML).

As of 2022, there are three leading treatments for SMA, including two drugs, nusinersen (Biogen trade name Spinraza) and risdiplam, and one gene therapy (onasemnogene abeparvovec), marketed by Novartis under the trade name Zolgensma. Zolgensma is approved for children less than two years old.

All available SMA treatments are effective and very expensive when acquired from the companies holding patents and regulatory exclusivities. In an ideal world, there would be extensive early screening and broad access to the gene therapy Zolgensma. But for many patients, there is no access to Zolgensma or they are over the age of 2 and not eligible for Zolgensma.

Among the two drugs, risdiplam has several advantages for the EML. While spinraza (nusinersen), requires an intrathecal injection every four months, risdiplam is orally administered and is taken once daily after a meal using the provided oral syringe. Since the administration of risdiplam requires no hospitalization and allows for the medication to be taken at home, it reduces the time and financial burden on patients and their caregivers. In addition, it reduces healthcare utilization costs and invasive procedures such as intrathecal injections, which carry certain risks and are not an option for many SMA patients due to underlying scoliosis. (1)

In addition, risdiplam offers the best chance to obtain a low-cost generic version in the near future. The drug is relatively inexpensive to manufacture. The regulatory pathway only requires providing evidence of bioequivalence. There are countries with GMP manufacturing capacity where the patents on risdiplam have not been filed or granted.

The listing of risdiplam is being sought for the core Essential Medicines List, although we recommend the WHO create a new category for expensive but important medicines and include a recommendation that governments take measures to obtain affordable versions of the drug. Risdiplam is an important example of the need to rethink the structure of the EML.

2. Relevant WHO technical department and focal point (if applicable).

N/A

3. Name of the organization(s) consulted and/or supporting the application

Knowledge Ecology International (KEI)

4. International Nonproprietary Name (INN) and Anatomical Therapeutic Chemical (ATC) code of the medicine.

INN: risdiplam

ATC code: M09AX10

6. Whether the listing is requested as an individual medicine or as representative of a pharmacological class.

The request for inclusion is for the spinal muscular atrophy (SMA) drug risdiplam.

**7. Treatment details (requirements for diagnosis, treatment and monitoring).
The application should specify the proposed therapeutic dosage regimen and duration of treatment.**

Risdiplam (originator trade name Evrysdi) is currently sold as a powder for oral solution 60mg/bottle 0.75mg/ml when reconstituted. The total volume when reconstituted is 80ml. Each ml of constituted solution contains 0.75mg of risdiplam. The drug can be distributed in powder form, and subsequently constituted as an oral solution with water. Once mixed with water, the solution is stored in a refrigerator and can be used for 64 days.

It is prescribed for oral daily use for pediatric and adult patients.

The dose depends upon age and weight. The current (September 21, 2022) recommended daily dosage by the U.S. FDA is as follows:

Less than 2 months of age	.15 mg/kg
2 months to less than 2 years of age	.2 mg/kg
2 years of age and older, weighing less than 20 kg	.25 mg/kg
2 years of age and older, weighing 20 kg or more	5 mg

The most common dose is 5 milligrams per day or 1.825 grams per year.

Risdiplam targets the underlying cause of SMA, and it must be taken for the duration of the individual's life.

Often the diagnosis of SMA begins with an in-office physical examination and review of family history. Signs of SMA include muscle weakness and hypotonia, motor difficulties, loss of motor skills, proximal muscle weakness, hyporeflexia (absence of reflexes), tongue fasciculations (involuntary twitches), and signs of low motor neuron disease. (2)

There are several genetic tests available that can identify SMA Types 1, 2, and 3. (3) Since 2018, SMA has been part of the Recommended Uniform Screening Panel (RUSP) in the US. As such, newborns are screened to identify possible mutations of the *SMN1* gene. (4) As of August 2022, 47 of 50 US states screen at birth for SMA. In some countries, such as Canada, newborn screening for SMA has also been added to the newborn screening panel (where they test the baby's blood for more than 25 treatable diseases). In Australia, since 2020, a number of jurisdictions offer newborn screening for SMA. (5) In these instances, such as in Canada and Australia, newborn screening tests are free to the patient. In Europe, several countries have implemented SMA screening in their newborn screening programs (e.g., Norway, Germany, Denmark, the Netherlands, and Poland).

8. Information supporting the public health relevance.

Spinal muscular atrophy (SMA) is a hereditary genetic disease caused by a defect or mutation in the *SMN1* gene. An estimated 2 percent of the population are considered carriers. Estimates of the incidence of SMA vary from 1 in 6,000 to 1 in 12,000 live births. (6–9) The data and research on the incidence of SMA is predominately from Europe and North America. SMA Type 1 is considered the most aggressive Type of SMA and is the leading genetic cause of death in early infancy. (10)

Patients with SMA have a malfunction of the *SMN1* gene, which means that patients have insufficient levels of survival motor neuron (SMN) protein. In turn, patients with SMA rely on the *SMN2* gene, which only produces about 10% of the functional SMN protein. (11) Risdiplam has the effect of correcting the defective part; the mechanism of action of risdiplam results in an increase in the number of full-length SMN proteins.

In many countries, risdiplam is considered a first-line treatment for patients who do not receive the gene therapy Zolgensma (onasemnogene abeparvovec), as a bridge between diagnosis and the administration of Zolgensma (1) (and in some cases, after receiving Zolgensma), and for later-onset SMA and patients who are not eligible for Zolgensma (onasemnogene abeparvovec) or Spinraza (nusinersen) due to age or physical ability.

Access to risdiplam is particularly critical for later-stage SMA types.

There are currently no SMA treatments included in the EML.

Like Biogen's Spinraza (nusinersen) and Novartis's Zolgensma (onasemnogene abeparvovec), Roche's branded version of risdiplam is expensive. A recent KEI survey found prices in high-income countries ranging from \$117 to \$232 per mg, or \$213,525 to \$423,400 annually for a dose of 5mg per day. (30) These prices do not account for non-transparent discounts and rebates to some third-party payers. Roche has offered some access programs in some lower-income countries to make risdiplam more affordable. For example, the approach in India is to limit the number of bottles the patient pays for in any given year, but the price is still very high relative to average incomes.

What makes risdiplam a particularly important drug is that, at present, it provides the best chance to make an affordable generic available. Not only is the drug easier to manufacture than Spinraza (nusinersen) or the gene therapy Zolgensma (onasemnogene abeparvovec), but risdiplam can be distributed in powder form through the mail. Caregivers of persons with SMA or SMA patients can reconstitute the drug in a water-based solution and administer the drug with simple oral/enteral syringes.

Risdiplam and Spinraza (nusinersen) are both appropriate for all ages and types of SMA. The gene therapy Zolgensma (onasemnogene abeparvovec) is an important treatment but is only recommended for children less than 2 years old.

KEI is currently in negotiations with companies that can manufacture generic versions of risdiplam.

9. Review of benefits: summary of evidence of comparative effectiveness.

The treatment, risdiplam, is a treatment for SMA itself. It is a disease-modifying therapy. Traditionally, there has only been care for the complications of SMA. For SMA patients who do not produce sufficient quantities of SMN protein, risdiplam works by creating SMN proteins.

There are currently two other disease-modifying therapies that treat SMA. Spinraza (nusinersen) is an *SMN2* targeting antisense oligonucleotide administered by intrathecal injection. It is indicated for pediatric and adult patients and has been investigated in two randomized controlled trials in pediatric patients aged 9 years or over. (12,13) The second is Zolgensma (onasemnogene abeparvovec), a gene therapy administered via an intravenous infusion. Zolgensma is indicated for the treatment of SMA patients of less than 2 years in the US and patients with Type 1 SMA or Type 3 or fewer *SMN2* copies in the EEA.

Risdiplam has several advantages compared to Spinraza (nusinersen) and Zolgensma (onasemnogene abeparvovec). In particular, it does not require hospitalization, reducing the time and financial burden on patients and their caregivers. Additionally, risdiplam is the first oral treatment for SMA, making it less intrusive and easy for patients (or their caregivers) to administer it themselves. Overall, the efficacy and safety were evaluated in clinical studies over a wide range of patients, from infants to adults.

Clinical Evidence

Major clinical trials, to date, for risdiplam include the SUNFISH trial in adults, the FIREFISH trial for infants, and the RAINBOWFISH trial. We summarize below these three trials for risdiplam.

FIREFISH

FIREFISH is an open-label, 2-part study to investigate the efficacy, safety, pharmacokinetics, and pharmacodynamics (PD) of Evrysdi in symptomatic Type 1 SMA patients (all patients had genetically confirmed disease with 2 copies of the *SMN2* gene). Part 1 of FIREFISH was designed as a dose-finding part of the study. The confirmatory Part 2 of the FIREFISH study assessed the efficacy of Evrysdi. Patients from Part 1 did not take part in Part 2.

In FIREFISH Part 1, 21 patients were enrolled. Their baseline characteristics were consistent with symptomatic patients with Type 1 SMA. The median age at enrollment was 6.7 months (range: 3.3-6.9 months) and the median time between the onset of symptoms and the first dose was 4.0 months (range: 2.0-5.8 months). A total of 17 patients received the therapeutic dose of risdiplam (the dose selected for Part 2). After 12 months of treatment, 41% of these patients were able to sit independently for at least 5 seconds. After 24 months of treatment, 3 more patients receiving the therapeutic dose were able to sit independently for at least 5 seconds, leading to a total of 59% achieving this motor milestone.

In FIREFISH Part 2, 41 patients with Type 1 SMA were enrolled. The median age of onset of clinical signs and symptoms of Type 1 SMA was 1.5 months (range: 1.0-3.0 months), 54% were female, 54% were described as Caucasian and 34% were described as Asian. The median age at enrolment was 5.3 months (range: 2.2-6.9 months) and the median time between the onset of symptoms and the first dose was 3.4 months (range: 1.0-6.0 months). At baseline, the median Children's Hospital of Philadelphia Infant Test for Neuromuscular Disease (CHOP-INTEND) score was 22.0 points (range: 8.0-37.0) and the median Hammersmith Infant Neurological Examination Module 2 (HINE-2) score was 1.0 (range: 0.0-5.0). At Month 24, 44% of patients achieved sitting without support for 30 seconds. Patients continued to achieve additional motor milestones as measured by the HINE-2: 80.5% were able to roll, and 27% of patients achieved a standing measure (12% supporting weight and 15% standing with support).

Overall, untreated patients with infantile-onset SMA would never be able to sit without support and only 25% would be expected to survive without permanent ventilation beyond 14 months of age. As a result, risdiplam treatment led to a significant improvement in motor function. Many infants achieved motor milestones that would never have been seen in untreated infants.

SUNFISH

SUNFISH was conducted in patients with Types 2 and 3 SMA from 2 to 25 years old. This trial included patients who, even though they have Type 2 or 3 of the disease, were unable to walk. Part 1 of SUNFISH was dose-finding and exploratory. Whereas Part 2 was a multicenter trial to investigate the efficacy, safety, pharmacokinetics, and pharmacodynamics of risdiplam.

In SUNFISH Part 1, 51 patients with Type 2 and 3 SMA (including 7 ambulatory patients) between 2 to 25 years of age were enrolled. After 1 year of treatment, there was a clinically meaningful improvement in motor function as measured by MFM-32 (this measure evaluates motor functions according to a number of predetermined assessments). The improvement in MFM-32 was maintained for up to 2 years on treatment.

SUNFISH Part 2 is the randomized, double-blinded, placebo-controlled portion of the SUNFISH study in 180 non-ambulant patients with Type 2 (71%) or Type 3 (29%) SMA. Patients were randomized with a 2:1 ratio to receive either Evrysdi at the therapeutic dose or placebo. Randomization was stratified by age group (2 to 5, 6 to 11, 12 to 17, 18 to 25 years old). The primary endpoint was the motor function assessment (MFM-32), which evaluates 32 items, including peripheral movements, upper limb movement, body axial movements, and lower limb movements. At baseline, 67% of patients had scoliosis (32% of patients with severe scoliosis). Patients had a mean baseline MFM-32 score of 46.1 and a Revised Upper Limb Module (RULM) score of 20.1. The baseline demographic characteristics were balanced between risdiplam and placebo arms with the exception of scoliosis (63% of patients in the risdiplam arm and 73% of patients in the placebo control).

For primary analysis for SUNFISH Part 2, the change from baseline in MFM-32 total score at Month 12, showed a clinically meaningful and statistically significant difference between

patients treated with risdiplam and placebo. Upon completion of 12 months of treatment, 117 patients continued to receive risdiplam. At the time of the 24-month analysis, the patients who were treated with risdiplam for 24 months overall experienced maintenance of improvement in motor function between month 12 and month 24.

RAINBOWFISH

RAINBOWFISH is an open-label, single-arm, multicenter clinical study to investigate the efficacy, safety, pharmacokinetics, and pharmacodynamics of risdiplam in infants up to 6 weeks of age. (14) These infants have been genetically diagnosed with SMA but do not yet present any symptoms. The primary analysis was conducted at 12 months in infants with two *SMN2* copies. The primary endpoint is the proportion of infants sitting without support for 5 or more seconds. Efficacy data from the study indicated that the infants reached a sufficient Children's Hospital of Philadelphia Infant Test for Neuromuscular Disease (CHOP-INTEND) score. CHOP-INTEND is a test that provides information on how strong a patient's muscles are and how well they can control these muscles. In addition, the infants maintained their swallowing and feeding abilities. Thus far, the study has shown that, following 12 months of treatment with risdiplam, the majority of pre-symptomatic infants met key milestones.

The RAINBOWFISH study's interim results have led the FDA to expand the indication for risdiplam to include the treatment of presymptomatic infants under 2 months of age with spinal muscular atrophy.

Comparisons of Risdiplam

We searched systematic reviews and assessment reports, and meta-analyses involving risdiplam. Unfortunately, there are no direct head-to-head studies comparing risdiplam against the two other existing treatments for SMA. As such, the only studies comparing risdiplam to Spinraza (nusinersen) and/or Zolgensma (onasemnogene abeparvovec) are indirect treatment comparisons. Below we summarize the four indirect comparison treatment studies that have included risdiplam.

2019 Indirect Comparison of Treatment

This study conducted a post-hoc indirect treatment comparison of Zolgensma (onasemnogene abeparvovec) and risdiplam using Children's Hospital of Philadelphia Infant Test for Neuromuscular Disease (CHOP-INTEND) scores. (15) The study concluded that, compared to risdiplam, Zolgensma (onasemnogene abeparvovec) improved CHOP-INTEND scores. While the study notes that the cohorts are not entirely matched with reference to their disease severity and age, the study still provides a useful comparison. Overall, they conclude that Zolgensma (onasemnogene abeparvovec) appears to be a more effective treatment in comparison to risdiplam.

2021 Indirect Comparison of Treatment

This study conducted an indirect comparison of treatment between risdiplam and Spinraza (nusinersen). (16) The author notes that due to the different baselines of the two trials used in the indirect treatment comparison, the author used "weighted" baseline characteristics to

match each other across the studies. The author concludes that both Spinraza (nusinersen) and risdiplam have had a major positive impact on the quality of life of patients with SMA. However, the matching adjusted indirect comparison indicates that risdiplam is more effective.

2022 Indirect Comparison of Treatment

This 2022 study, funded by Roche, used risdiplam and compared two instances of Spinraza (nusinersen) and Zolgensma (onasemnogene abeparvovec) using unanchored population-adjusted indirect comparison methodologies, with known prognostic and predictive variables. (17) This is the only population-adjusted indirect comparison treatment to compare risdiplam.

Risdiplam versus Spinraza (nusinersen). The study concluded, with this comparison, that risdiplam may improve the achievement of motor milestones compared to nusinersen. The comparison also reported a lower likelihood of serious adverse events with risdiplam compared with nusinersen, despite risdiplam having a longer follow-up. They noted that this may represent better efficacy for risdiplam because there were similar serious adverse events observed in both trials. Since studies of risdiplam and Spinraza (nusinersen) included similar populations, the comparison found overall improved survival and motor function with risdiplam for Type 1 SMA. Comparing risdiplam with Spinraza (nusinersen) in Types 2 or 3 SMA was challenging due to the large differences in population. As a result, the study could not draw concrete conclusions from indirect comparison with Types 2 and 3 SMA.

Risdiplam versus Zolgensma (onasemnogene abeparvovec). The paper concluded that the analysis did not provide sufficient evidence to draw conclusions on the relative efficacy between the two treatments. This was due to the substantial differences in study populations.

IQWiG

In 2021, the German Institute for Quality and Efficiency in Health Care (IQWiG) examined whether risdiplam has an advantage in comparison to the best supportive care and Spinraza (nusinersen). (18) Since no direct comparisons were available, the IQWiG conducted an indirect comparison of nusinersen and risdiplam studies. These comparisons, as noted earlier, are fundamentally not reliable. Despite this, the IQWiG concluded that there are no reliable differences between risdiplam and nusinersen. They do note, however, that there is one advantage to risdiplam. Namely, that long-term ventilation is necessary less often. As a result, they conclude that they cannot make a statement about the advantage of risdiplam versus nusinersen.

10. Review of harms and toxicity: summary of evidence of safety.

Risdiplam is approved for the treatment of spinal muscular atrophy in pediatric patients, and adults. There are no black box warnings for risdiplam. Discussions on the safety, toxicity, and adverse events (AE) follow below.

Later-Onset SMA

The safety of risdiplam in later-onset SMA was based on the data from a randomized, double-blinded, placebo-controlled study in patients with SMA Type 2 and Type 3 (n=180). The patient population age ranged from 2 years to 25 years at the time of the initial dose.

The most common AE was fever, diarrhea, and a rash. These AE were reported in less than 10% of the patients that received risdiplam. AE that occurred in at least 5% of patients treated with risdiplam and at an incidence of $\geq 5\%$ greater than on placebo related to fever (22% vs 17%), diarrhea (17% vs 8%), rash (17% vs 2%), mouth and aphthous ulcers (7% vs 0%), arthralgia (5% vs 0%), and urinary tract infection (5% vs 0%).

Infantile-Onset SMA

The safety of risdiplam in pre-symptomatic SMA is based on data from an open-label single-arm study. The patient population ranged in age from 2 months to 7 months at the time of the first dose. Their weight ranged from 4.1kg to 10.6kg.

The most frequent adverse reactions reported were similar to those in the later-onset SMA patients. In addition to the above-reported ones, the following adverse reactions were reported in $\geq 10\%$ of patients: upper respiratory tract infection (including nasopharyngitis, rhinitis), lower respiratory tract infection (including pneumonia, bronchitis), constipation, vomiting, and cough.

Pre-Symptomatic SMA

The safety of risdiplam in pre-symptomatic SMA is based on an open-label single-arm study. The study enrolled patients between 16 and 40 days of age at the time of their first dose. The safety profile in pre-symptomatic patients is consistent with the profile for symptomatic patients treated with risdiplam.

Comparative Safety of Risdiplam

One academic study has examined the safety of risdiplam through an indirect treatment comparison study comparing risdiplam to Spinraza (nusinersen) and the best supportive care. (17) The table below (Table 1) summarizes the results of the unadjusted comparison and matching-adjusted indirect comparison (MIAC) comparison on the reporting of serious adverse events (SEA). The authors concluded that there was a lower likelihood of reporting SAEs with risdiplam versus Spinraza (nusinersen), despite there being a longer follow-up time for risdiplam. The authors did note, however, that this could mean risdiplam has better efficacy and not necessarily safety.

Table 1: Safety comparison risdiplam

Milestone	Comparator (STUDY)	Unadjusted comparison		MAIC	
		Responders/sample size, n (% responders [95% CI])	OR for risdiplam against comparator (95% CI)	Responders/sum of weights, weighted n (% responders [95% CI])	OR for risdiplam against comparator (95% CI)
Safety Any SAE	Risdiplam (FIREFISH)	33/58 (57% [43–69] [§])	–	24.38/44.42 (55% [36–72] [§])	–
	Nusinersen (ENDEAR)	61/80 (76% [65–85] [§])	0.411 (0.189–0.881)	61/80 (76% [65–85] [§])	0.379 (0.146–0.971)
	BSC (ENDEAR)	39/41 (95% [84–99] [§])	0.068 (0.014–0.211)	39/41 (95% [84–99] [§])	0.062 (0.011–0.228)

[†]FIREFISH HINE-2 motor milestone achievement in infants assessed at the later of Days 0, 119, 245 and 364.
[‡]ENDEAR HINE-2 motor milestone achievement assessed in infants at the later of Days 183, 302 and 394.
[§]Clopper–Pearson CIs.
[¶]ORs calculated using half-cell correction.
^{*}No ORs were calculated due to 0 events in both arms.
^{††}Data were taken from an interim analysis (n = 51).
^{‡‡}FIREFISH CHOP-INTEND score assessed at the later of Days 0, 119, 182, 245, 301, 364 and 427.
^{§§}ENDEAR CHOP-INTEND score assessed at the later of Days 183, 302 and 394.
OR >1 favor risdiplam over comparator for efficacy outcomes; OR <1 favor risdiplam over comparator for safety outcomes. Bootstrap; N = 1000 Samples.
BSC: Best supportive care; CHOP-INTEND: Children’s Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HINE-2: Hammersmith Infant Neurological Examination, Section 2;
MAIC: Matching-adjusted indirect comparison; NA: Not available; OR: Odds ratio; SAE: Serious adverse event.

When comparing Spinraza (nusinersen) and risdiplam for Type 2 and 3 SMA, the authors concluded that the data and analyses were insufficient to draw conclusions on the safety.

Despite the study’s conclusion, it is necessary to review the limitations of their comparison. The study examined aggregated SAEs numbers but did not perform a more in-depth assessment of the individual SAEs. For example, it did not compare or examine how manageable and easily resolved the individual SAEs were across the comparison categories. In addition, Roche funded the study, and all the study contributors are employees of Roche and are stockholders in Roche.

11. Summary of available data on comparative cost and cost-effectiveness of the medicine.

Cost-Effectiveness Analyses

One of the challenges of presenting evidence regarding the cost-effectiveness of treatment for purposes of inclusion in the EML is the fact that many existing studies provide an analysis for use in a high-income country, and not in lower-income countries where the EML will be in practice most relevant.

Another challenge in evaluating cost-effectiveness studies is the lack of studies that consider the cost-effectiveness of drugs if their price were to be dramatically reduced, by, for example, states using exceptions in patent laws or other measures to obtain low-cost generic versions.

All the studies cited below suffer from one or both two weaknesses, in terms of considering a product for the EML.

CADTH

The Canadian Agency for Drugs and Technologies in Health (CADTH) concluded that:

“Should risdiplam be considered equally effective to nusinersen, it is likely to result in fewer drug acquisition costs and may represent a cost-effective option in populations where nusinersen would be displaced, assuming the list price of nusinersen is what is currently paid by public drug plans.” (1)

Further, when considering whether to reimburse nusinersen, CADTH noted that:

“[R]isdiplam was expected to cost savings among patients with SMA type 1 (i.e., risdiplam cost saving), but this reduction was outweighed by the additional cost among patients with SMA type 2 and 3.” (19)

NICE

The National Institute for Health and Care Excellence (NICE) from the United Kingdom noted that there is no clinical or cost-effectiveness evidence for patients who have had nusinersen. The committee did agree, however, that the clinical trials demonstrated that risdiplam meaningfully improves motor functions for people with Type 1, 2, and 3 SMA. They concluded that risdiplam could not be recommended at this time because it is not likely to be a cost-effective use of National Health Service (NHS) resources. Despite NICE not recommending risdiplam for routine use, they acknowledge the unmet need for effective treatments for SMA. As a result, risdiplam is recommended through a managed access agreement (20). The managed access agreement in the UK was created for drugs or treatments that show potential but where there remains uncertainty on the long-term benefits.

NCPE

Ireland’s National Centre for Pharmacoeconomics (NCPE) concluded that risdiplam is not recommended for reimbursement until cost-effectiveness was improved. In particular, they noted:

“The price to wholesalers of risdiplam (60mg/80ml) is €8,450 per bottle (list price), with an annual per-patient drug cost to the HSE estimated at €264,371. The Applicant’s estimated 5 year gross budget impact for risdiplam was €107 million compared to €132m for nusinersen (this does not take into account the PAS in place for nusinersen) for SMA Type 1, 2, and 3. It is unclear what proportion of patients may switch to risdiplam following treatment with the other disease-modifying therapies (due to mode of administration/loss of efficacy etc.), as this was not calculated by the Applicant.” (21)

Zorginstituut Nederland

The Dutch health technology assessment for Risdiplam concluded that the price of risdiplam is too high to reimburse in the Dutch basic insurance package. (22) This decision was justified because of the uncertainty about the cost-effectiveness, in particular, of the long-term effects, utilities, and cost estimates. In addition, they noted the price per patient per year would be EUR 256,853.

When conducting cost-effectiveness analyses the Zorginstituut was unable to take into account the cost-effectiveness of Zolgensma (onasemnogene abeparvovec) and Spinraza (nusinersen) since there was an absence of data on the comparison and that future treatment dynamics are difficult to predict. They calculated that SMA Type 1 is EUR 362,300 per QALY and SMA Type 2 and 3 is EUR 416,471 per QALY. Yet, with the Zorginstituut's reference value of EUR 80,000 per QALY, they conclude that risdiplam is not cost-effective. For it to qualify as cost-effective, it would need to decrease by 94% for SMA Type 1 and 78% for SMA Types 2 and 3.

Academic Assessment

There is one academic cost-effectiveness study of risdiplam. The study examined risdiplam versus Spinraza (nusinersen) for the treatment of SMA Type 1 patients in China. (23) The study concluded that:

“Patients treated with risdiplam gained 1.42 more life-years and 1.41 more QALYs compared to nusinersen. The total direct medical costs of treating with risdiplam is CNY 207,486 lower than treating with nusinersen. Thus, risdiplam is dominant over nusinersen in treating patients with SMA type 1.”

The following two tables (Table 2 and Table 3) show cost comparisons of risdiplam with the two other existing SMA treatments. The first is a table (Table 2) Knowledge Ecology International compiled indicating the price of all three SMA treatments per year in USD. The second table (Table 3) is one developed by CADTH, which demonstrates a similar daily cost of Spinraza (nusinersen) and risdiplam after the second year. (1)

Table 2: Cost comparison of current SMA treatments

Brand Name	INN	Price
Evrysdi	Risdiplam	Up to 340,00 USD a year
Zolgensma	Onasemnogene abeparvovec	2,125,000 USD (single injection)
Spinraza	Nusinersen	750,000 USD for the first year and 375,000 USD annually for all subsequent years

Table 3: CADTH SMA cost comparison

Treatment	Strength	Form	Price	Age and weight	Recommended dosage ^a	Daily cost	Annual cost
Risdiplam (EVRYSDI)	60 mg	Powder for oral solution	\$11,638.3500 ^b	2 months to < 2 years of age	0.20 mg/kg daily	\$256.04 ^c	\$93,456
				≥ 2 years and < 20 kg	0.25 mg/kg daily	\$918.94 ^d	\$335,415
				≥ 2 years and ≥ 20 kg	5 mg daily	\$969.86	\$354,000
Antisense oligonucleotide (ASO)							
Nusinersen (Spinraza)-first year	12 mg / 5 mL	Injection	\$118,000.0000 ^e	NA	6 injections per year	\$1,939.73	\$708,000
					3 injections per year	\$969.86	\$354,000
-subsequent years							

Note: Prices do not include dispensing fees. Annual prices are based on 365 days per year.

^aRecommended dosages are from the respective product monographs, unless otherwise indicated.¹³

^bSponsor's submitted price.¹

^cBased on a median patient weight of 6.60 kg from the FIREFISH trial.¹⁴

^dBased on a mean patient weight of 18.95 kg calculated by the sponsor using SMA-specific growth curves.¹⁵

^eOntario Exceptional Access Program (EAP) formulary (accessed December 2020).¹⁶

Costs of Manufacturing Risdiplam

The most important component of the manufacturing cost of the drug is the cost of the active pharmaceutical ingredient (API). This cost depends on the price and quantity required.

The quantities of both risdiplam and nusinersen are both small. The most common dose of risdiplam is 5 mg per day or 1.825 grams per year. For comparison, the standard dose for a leading HIV treatment, dolutegravir/lamivudine/tenofovir, is 50+300+300 = 650 mg per day, or 237.25 grams per year. Efavirenz/lamivudine/tenofovir is 600+300+300 = 1200 mg per day, or 438 grams per year.

The prices of the API depend upon the methods used to manufacture the drug as well as the scale of production and the degree of competition among suppliers.

At present, there are a number of suppliers of the risdiplam API, which sell small quantities for research purposes. The prices quoted are often for very small quantities, and do not represent the much lower prices that are possible for larger orders. The fact that several companies are selling risdiplam does illustrate the low know-how barriers to entry.

KEI expects that in a competitive market, the risdiplam API can be manufactured at prices from USD \$4,000 to \$40,000 per kg, or \$4 to \$40 per gram, depending on the scale of production.

These estimates are based on KEI's confidential discussions with manufacturers. The high estimate is double the highest estimate KEI received from one potential supplier.

The raw materials costs have been estimated at \$1,700 per kg, and the conversion costs are dependent upon scale. At reasonably large-scale production, conversion costs could fall to less than \$3,000 per kg, but at very small-scale production, conversion costs would be significantly higher.

For comparisons regarding API costs, in 2018, Hill, Barber, and Gotham published a paper estimating the costs of production and potential prices for the WHO Essential Medicines List in the *British Medical Journal* (24). Hill, Barber, and Gotham estimated a wide range of API prices per kilogram. In a spreadsheet available from [this link](#), KEI lists the 125 drugs on the WHO EML for which Hill, Barber, and Gotham have estimated prices for API per kg. The estimated API prices vary considerably, from \$2/kg to \$669,376/kg, the last price being an extreme outlier. While there is a huge range of prices, 98 percent of the prices are less than \$10,000/kg, 83 percent are less than \$1,000/kg and 38 percent are less than \$100/kg. Only 3 of the 125 products have an API price per kg of more than \$10,000. According to their study, the median API price is \$152/kg.

The WHO EML list has a clear bias toward older small molecule products with large patient populations, and thus, the lower price per kg for the API is not expected to be representative of a small molecule drug with a very small scale of production.

A KEI consultant has looked at drugs with similar demand using actual import-export data to support our estimate of \$4,000-\$40,000/kg. (25)

A generic version of risdiplam will likely have a small scale of production initially for three reasons: first, the prevalence of the disease is small, second, the drug is patented by Roche in much of the world, and lastly, the annual dose is quite small.

While the generic price per API for risdiplam is likely to be far higher than the median price for drugs on the WHO EML, it will still be low enough to result in far more affordable versions of the drug.

The current price of risdiplam per unit of API in high-income countries is extremely high. On a kilogram of API basis, the Roche price in high-income countries ranges from \$118,000,000 per kilogram to \$209,000,000 per kilogram. Even if the generic price for the API was an order of magnitude higher than our upper estimate for the API cost (\$400,000), it would still make it possible to manufacture the drug for less than one-half of a percent of the U.S. list price and make the drug widely available even without supplementary insurance or other third-party reimbursements.

Summary of available data on cost-effectiveness

The national cost-effectiveness analyses concluded that due to the limited studies comparing the efficacy of nusinersen or risdiplam it was difficult to conclude the cost-effectiveness of risdiplam. Despite this, CADTH reasoned that risdiplam was expected to contribute to cost savings. This is a similar conclusion that the only academic study examining the cost-effectiveness of risdiplam reached. On the other hand, the Dutch Zorginstituut, NICE, and NCPE concluded that risdiplam could not be recommended because of the drug's excessive price. In other words, it would not be considered a cost-effective use of public health resources. Overall, the above national reviews of cost-effectiveness agree that risdiplam, if made more affordable, would be recommended.

Overall, Roche's risdiplam is expensive. A recent KEI survey found prices in high-income countries range from \$117 to \$232 per milligram or \$213,525 to \$423,400 annually for a

dose of 5 milligrams per day. (26) There are undoubtedly non-transparent discounts and rebates to some third-party payers. Roche has offered some programs in some lower-income countries to make products more affordable. For example, the approach in India is to limit the number of bottles the patient pays for in any given year.

If generic suppliers enter the market, prices for risdiplam will fall, dramatically. None of the current cost-effectiveness analyses considered a scenario where less expensive versions are available, even though this is a small molecule drug with few know-how barriers to manufacture.

The WHO needs to consider the cost-effectiveness of Roche's risdiplam (Evrysdi) both at its current high price and for reasonable scenarios for generic entrants to make an affordable version of risdiplam available.

12. Summary of regulatory status and market availability of the medicine.

Risdiplam is available worldwide and approved in 81 countries. In addition, marketing authorization has been filed in a number of additional countries. In all jurisdictions where risdiplam has been approved, it is indicated for the treatment of spinal muscular atrophy in pediatric and adult patients of 2 months and older. Recently, the FDA (USA) expanded this initial indication for risdiplam to include the treatment of presymptomatic babies under 2 months old with SMA. (27)

There are currently no generic manufacturers producing risdiplam.

Roche and PTC Therapeutics, Inc. have filed numerous patents covering risdiplam. In the U.S. FDA Orange Book, Roche lists two patents, each titled "Compounds for treating spinal muscular atrophy" and each assigned to Roche and PTC Therapeutics.

- 9586955, <https://patents.google.com/patent/US9586955B2/en?q=9586955>
- 9969754, <https://patents.google.com/patent/US9969754B2/en?q=9969754>

The World Intellectual Property Organization (WIPO) Patent Cooperation Treaty (PCT) equivalent versions are:

- PCT/US2013/025292,
<https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2013119916&fid=SG192215365>
- PCT/EP2015/060343
<https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2015173181&cid=P12-LAHC2C-71298-1>

The WIPO PCT applications identify where patents have been filed at the national level through the PCT process. There are 156 contracting states in the PCT, but a much smaller number of governments where the two risdiplam patents have entered the PCT national phase.

The ANNEX on risdiplam WIPO PCT patent applications provides information on where the two patents that are listed in the US FDA Orange Book have entered the national phase, according to WIPO, as of November 14, 2022. According to WIPO, Roche has filed at least one of the two patents in 22 national offices, as well as in the European Patent Office (EPO) and the Eurasian Patent Organization (EAPO). In 14 of the 22 national offices, at least one of the two patents has been granted. WIPO also notes that the EPO and the EAPO have granted at least one of the patents. The EPO provides examinations for 39 European member states, one extension state, and four validation states. The EAPO members are the Republics of Azerbaijan, Armenia, Belarus, Georgia, Kazakhstan, Kyrgyz, Moldova and Tajikistan, and the Russian Federation.

The Roche PCT filings for these two patents do include several lower- and middle-income countries with significant manufacturing capacity, including, for example, India, Brazil, Indonesia, and Thailand. However, there are also several countries that have manufacturing capacity where no WIPO patent applications have entered the national phase.

Some countries, like Argentina, are not members of the PCT, and patents can be filed at the national level independent of the PCT. Roche may assert other patents than those listed in the US FDA Orange Book in other jurisdictions as well.

In addition to whatever rights Roche and or PTC Therapeutics have in patented inventions, Roche has regulatory rights in data and orphan drug exclusivity in several jurisdictions. These exclusivities create additional barriers to generic suppliers from entering the market.

Currently, there are no existing or planned licensing agreements with generic manufacturers.

KEI had earlier requested a voluntary license from Roche to manufacture and sell a generic version of risdiplam. (28) On August 5, 2022, Roche rejected the request for a voluntary license.

KEI is currently investigating manufacturing risdiplam from a country where rights in patented inventions, data, or regulatory approval do not present a barrier.

KEI has identified qualified manufacturers in countries where Roche or PTC Therapeutics do not appear to have patent protection. KEI has asked Roche to provide more information on its risdiplam patent landscape to provide greater certainty.

For many families, even those living in a country with risdiplam patents approved, it will be possible for the families to import the drug for personal use, or for compounding pharmacies to make the drug available to patients.

Of the 81 countries where risdiplam is marketed, Roche's risdiplam is only reimbursed in 17 countries. The astronomical price of risdiplam renders the drug largely inaccessible in countries where it is not reimbursed.

Risdiplam is only a realistic form of treatment for SMA patients that reside in higher-income countries (i.e., where risdiplam is reimbursed, such as the USA, Australia, France, Italy, England, Scotland, Norway, and Japan). Thus, while risdiplam is an essential product to

treat SMA and is marketed globally, it is only available to a select few patients who happen to belong to national health programs that can afford the high cost of risdiplam.

13. There is a pressing need for a new EML category for products that should be made accessible if available at affordable prices

The current structure of the EML is not designed to deal rationally and effectively with pricing and affordability issues. KEI has repeatedly asked the WHO to create a category for products that would be considered essential if available at affordable prices and to acknowledge the agency governments must influence prices.

The risdiplam case is a clear illustration of the need for such a category. Roche sells the drug \$117 million to \$200 million per kg of API, which results in an annual cost to patients that is excessive. But risdiplam can be manufactured at a very small fraction of this price. Any decision to list risdiplam on the EML which does not recognize both the high price from Roche and the opportunities for lower generic prices ignores two of the most important facts relevant to third-party payers and patients.

The following are some of the examples where KEI has asked the WHO to create a category in the EML for drugs that are medically important, and which should be accessible if available at affordable prices.

- 2007, March 2. KEI asked the WHO Expert Committee on the Selection and Use of Essential Medicines and the WHO Department of Medicines Policy and Standards “to create a new category in the 'WHO Model List of Essential Medicines' (EML) for products that would be essential “if available from competitive generic suppliers at generic prices.” (29)
- 2012, February 28. KEI submission to the WIPO Standing Committee on the Law of Patents (SCP) on Patents and Health, asks WIPO members, “What would the WHO EML look like if there was a new category for products that are cost effective if available from generic suppliers?” (30)
- 2013, January 14. Proposal for the inclusion of trastuzumab in the WHO Model List of Essential Medicines for the treatment of HER-2 positive breast cancer. KEI requested the WHO Expert Committee on the Selection and Use of Essential Medicines to “identify the measures that will be necessary to expand access to the drug at affordable prices, including the measures necessary to overcome intellectual property barriers, a biosimilar pathway for drug registration, including a WHO prequalification process for trastuzumab, and also the efficient procurement strategies that have proved to be useful in bringing down prices for HIV drugs.” (31)
- 2015, April 20. At the Open Session of the 20th Expert Committee on the Selection and Use of Essential Medicines, KEI reiterates its proposal that the WHO create a category in the EML for products that would be essential, if available at affordable prices. (32)

- 2016, December. A KEI proposal for the inclusion of enzalutamide in the WHO Model List of Essential Medicines of the treatment of metastatic castration resistant prostate cancer requested the WHO to “consider the cost effectiveness of the drug when available from competitive generic suppliers.” (33)
- 2016. December. The KEI Proposal for The Inclusion Of Trastuzumab Emtansine (T-DM1) In the Who Model List of Essential Medicines for the Treatment of HER2-Positive Locally Advanced or Metastatic Breast Cancer stated: “For the WHO to consider a recommendation on T-DM1, it is important to consider the possibility of biosimilar products . . .” (34)
- 2017, March 27. A KEI statement at the 21st meeting of the WHO Expert Committee on the Selection and Use of Essential Medicines, asked for a new EML category for drugs that are medically essential but face challenges regarding affordability, noting that governments and patients would take this as a signal to implement policies to make these medically effective drugs affordable. (35)
- 2017, October 13. KEI provided comments to WHO Director General Tedros on the Draft Concept Note Concerning the WHO General Programme of Work. KEI noted that “The WHO Expert Committee has been asked, several times, to create a category in the EML for products that would be essential, if available at affordable prices. If drugs are medically effective, but expensive, they should be placed in an EML category for drugs that are medically essential but face challenges regarding affordability. Governments and patients would take this as a signal to implement policies to make these medically effective drugs affordable.” (36)
- 2019, January. Proposal for the inclusion of enzalutamide and abiraterone acetate in the WHO Model List of Essential Medicines for the treatment of metastatic castration-resistant prostate cancer. KEI requested the WHO to “consider the cost-effectiveness both for cases where the drugs are expensive, from the originator, and when the drugs are less expensive from generic suppliers, including looking at reasonable scenarios for generic prices falling over time.” (37)
- 2019, April 1. A KEI statement to the 22nd meeting of the WHO Expert Committee on the Selection and Use of Essential Medicines states “[i]f drugs are medically effective, but expensive, they should be placed in an EML category for drugs that are medically essential but face challenges regarding affordability. Governments and patients would take this as a signal to implement policies to make these medically effective therapies affordable. A system of medical guidance that consistently ignores or excludes new drugs for cancer needs to be reformed, and new options for dealing with affordability and access are needed if we are serious about achieving equality of health outcomes.” (38)
- 2020, December. Proposal for the inclusion of enzalutamide in the WHO Model List of Essential Medicines for the Treatment of Metastatic Castration-Resistant Prostate Cancer. KEI requested the WHO to “consider the cost-effectiveness for both cases: when the drugs are expensive (from the originator), and when the drugs are less

expensive (from generic suppliers), including looking at reasonable scenarios for generic prices falling over time.” (39)

- 2021, April 29. KEI made a presentation to the WHO Essential Medicines List Cancer Medicines Working Group, noting “[t]he WHO EML evaluation deals with efficacy directly, but prices indirectly, often on an *ad hoc* basis, or not at all, despite the relevance and importance to users of the list.” KEI notes that “prices for products are not a state of nature, policies can make a difference.” KEI proposes the WHO separate the evaluation of efficacy and prices, and (1) Identify medicines that are useful medically, (2) include on the EML main list products that are both medically useful and already affordable, and (3) include a new category for products that are medically useful, but that may have high prices, and that should be added to a national list when and if measures are undertaken to acquire products at affordable prices.” (40)
- 2021, June 21. KEI made a statement to the Open Session of the 23rd Meeting of the WHO Expert Committee on the Selection and Use of Essential Medicines. The WHO Expert Committee has been asked, several times, to create a category in the EML for products that would be essential, if available at affordable prices. A pathway for affordable antineoplastics would expand treatment options for patients, including the inclusion of second-line treatments. . . . If drugs are medically effective, but expensive, they should be placed in an EML category for drugs that are medically essential but face challenges regarding affordability. Governments and patients would take this as a signal to implement policies to make these medically effective therapies affordable.” (41)
- 2022, January 26. KEI made a statement on the Political declaration of the third high-level meeting of the General Assembly on the prevention and control of non-communicable diseases and WHO’s roadmap for the global action plan for the prevention and control of NCDs at the 150th session of the World Health Organization’s Executive Board. KEI proposes the Executive board support the establishment of a standing EML Working Group on pricing and consider a category for “effective but expensive category of drugs, including policy interventions that can make products more affordable.” (42)

A recent paper in JAMA, while not citing KEI’s work, makes a similar recommendation, for “a more rigorous and systematic process for considering cost-effectiveness and affordability issues.” (43)

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ANNEX

Table 4: National phase filings for two Roche WIPO PCT risdiplam patent applications, as of November 14, 2022.

Country	Patents Filed	PCT/EP2015 / 060343 Granted*	PCT/US2013 / 025292 Granted*	Per capita GNI in 2020 (Atlas method)
Australia	PCT/EP2015/060343 PCT/US2013/025292	22/08/2019	16/11/2017	\$53,680
Brazil	PCT/EP2015/060343 PCT/US2013/025292	-	-	\$7,800
Canada	PCT/EP2015/060343 PCT/US2013/025292	-	16/02/2021	\$43,540
Chile	PCT/EP2015/060343	-	-	\$13,120
China	PCT/EP2015/060343	-	-	\$10,530
Colombia	PCT/EP2015/060343 PCT/US2013/025292	14/06/2018	19/05/2017	\$5,830
Costa Rica	PCT/EP2015/060343 PCT/US2013/025292	07/09/2022	-	\$11,580
Ecuador	PCT/US2013/025292	-	-	\$5,540
India	PCT/EP2015/060343	13/03/2020	-	\$1,910
Indonesia	PCT/US2013/025292	-	-	\$3,870
Israel	PCT/EP2015/060343 PCT/US2013/025292	-	01/03/2018	\$42,610
Japan	PCT/EP2015/060343 PCT/US2013/025292	-	-	\$40,810
Mexico	PCT/EP2015/060343 PCT/US2013/025292	14/01/2020	12/02/2019	\$8,530
New Zealand	PCT/EP2015/060343 PCT/US2013/025292	03/03/2020	01/07/2016	\$41,480
Peru	PCT/EP2015/060343	14/06/2018	-	\$6,060
Philippines	PCT/EP2015/060343 PCT/US2013/025292	-	-	\$3,430
Republic of Korea	PCT/EP2015/060343 PCT/US2013/025292	-	04/08/2020	\$32,930
Serbia	PCT/EP2015/060343	31/01/2020	-	\$7,430
Singapore	PCT/EP2015/060343	02/06/2020	-	\$55,010
Thailand	PCT/EP2015/060343 PCT/US2013/025292	-	-	\$7,070
Ukraine	PCT/EP2015/060343 PCT/US2013/025292	-	11/06/2018	\$3,570
United States of America	PCT/US2013/025292	-	07/03/2017	\$64,140

Country	Patents Filed	PCT/EP2015 / 060343 Granted*	PCT/US2013 / 025292 Granted*	Per capita GNI in 2020 (Atlas method)
Eurasian Patent Organization	PCT/EP2015/060343 PCT/US2013/025292	30/04/2020	30/04/2018	n/a
European Patent Office	PCT/EP2015/060343 PCT/US2013/025292		27/06/2018	n/a