Risdiplam (Evrysdi®) for the treatment of 5q spinal muscular atrophy (SMA) in patients 2 months of age and older, with a clinical diagnosis of SMA Type 1, 2 or 3 or with one to four SMN2 copies.

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost-effectiveness of risdiplam for the treatment of 5q SMA in patients 2 months of age and older, with a clinical diagnosis of SMA Type 1, 2 or 3 or with one to four SMN2 copies. Following assessment of the Applicant's submission, the NCPE recommends that risdiplam not be considered for reimbursement until cost-effectiveness can be improved relative to existing treatments*. This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013. The HSE asked the NCPE to carry out an evaluation of the Applicant's (Roche Products Ireland) Health Technology Assessment dossier on risdiplam. The NCPE uses a decision framework to systematically assess whether a technology is cost-effective. This includes clinical effectiveness and health related quality of life benefits, which the new treatment may provide and whether the cost requested by the pharmaceutical company is justified.

Following the recommendation from the NCPE, the HSE examines all the evidence which may be relevant for the decision; the final decision on reimbursement is made by the HSE. In the case of cancer drugs, the NCPE recommendation is also considered by the National Cancer Control Programme (NCCP) Technology Review Group.

About the National Centre for Pharmacoeconomics

The NCPE are a team of clinicians, pharmacists, pharmacologists and statisticians who evaluate the benefit and costs of medical technologies and provide advice to the HSE. We also obtain valuable support from clinicians with expertise in the specific clinical area under consideration. Our aim is to provide impartial advice to help decision makers provide the most effective, safe and value for money treatments for patients. Our advice is for consideration by anyone who has a responsibility for commissioning or providing healthcare, public health or social care services.

National Centre for Pharmacoeconomics **March 2022**

Summary

On the 30th of July 2021, Roche Products Ireland submitted a health technology assessment dossier on risdiplam (Evrysdi®) for the treatment of 5q spinal muscular atrophy (SMA) in patients 2 months of age and older, with a clinical diagnosis of SMA Type 1, 2 or 3 or with one to four SMN2 copies. Risdiplam is designated an orphan medicine.

SMA is a rare, monogenic neuromuscular disorder resulting in severe weakness of the limbs, trunk, bulbar and respiratory muscles secondary to failure to gain and maintain functional motor nerve innervation of skeletal muscles. The severity of SMA is highly variable and patients with heterogeneous clinical features can be classified into different phenotypes on the basis of age at onset and the most advanced motor milestone achieved during development. Approximately 99% of patients with SMA have Types 1, 2 or 3. The focus of the Applicant's submission was treatment with risdiplam in SMA Types 1 to 3 inclusive. Natural history of the disease demonstrates that 50% of infants with SMA Type 1, who have 2 copies of the SMN2 gene, will die or require permanent daily non-invasive ventilation support by 10.5 months of age. For patients with SMA Type 2, natural history indicates that without treatment these children have a progressive decline in motor function over time, most prominently during the ages of 6 to 16 years. In patients with SMA Type 3, there is also a progressive decline in motor function over time without treatment, most prominently during the age of 10 to 15 years.
Patient outcomes are monitored using a number of different scales which measure developmental milestones which are largely centred on motor function. Measurement scales, while being similar, differ slightly and are not all consistently used in the clinical trials of SMA treatments. These include CHOP-INTEND, HINE-2, MFM-32, RULM and HFMSE.

Risdiplam comes as a 0.75 mg/mL powder for oral solution. It is taken orally once a day. The recommended once daily dose of risdiplam is determined by age and body weight.

- 2 months to < 2 years of age: 0.2 mg/kg body weight
- ≥ 2 years of age and < 20 kg: 0.25 mg/kg body weight
- ≥ 2 years of age and ≥ 20 kg: 5mg (fixed).

The safety and efficacy of risdiplam in paediatric patients < 2 months of age have not yet been established. Treatment can be continued indefinitely.

Prior to the availability of disease modifying treatments, management of SMA consisted mainly of best supportive care (BSC) (i.e. supportive, rehabilitative and palliative care to treat or prevent complications of muscle weakness and maintain quality of life). Nusinersen and onasemnogene abeparovec are disease modifying treatments. Nusinersen is reimbursed, in Ireland, for the treatment of SMA Type 1, 2 and 3 in patients aged under 18 years. Onasemnogene abeparovec is reimbursed, in Ireland, for patients with a confirmed diagnosis of 5q SMA with a bi-allelic mutation in the SMN1 gene and a clinical diagnosis of SMA Type 1, or a confirmed diagnosis of pre-symptomatic 5q SMA with a bi-allelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene. Confirmation of age at onset of symptoms is also a condition of reimbursement, given that there is limited evidence in patients 2 years of age or older. In the dossier for this submission, the Applicant considered the disease modifying treatments (nusinersen and onasemnogene abeparovec), as well as BSC as the relevant comparators.

1. Clinical Evidence

The clinical trial programme for risdiplam comprises four clinical trials; FIREFISH conducted in infants (aged 1 to 7 months at enrolment) with SMA Type 1 and; SUNFISH conducted in patients with SMA Type 2 or 3. The clinical programme for risdiplam is further supported by safety data from (i) the on-going JEWELFISH study in paediatric and adult patients with SMA who were previously treated with a disease-modifying therapy (which included onasemnogene abeparovec); (ii) the RAINBOWFISH study, a multi-centre, open-label, single-arm, phase II study of risdiplam in infants (from birth to 6 weeks of age) who have been genetically diagnosed with SMA, but are pre-symptomatic.

SMA Type 1

FIREFISH was an open label, two-part, multi-centre, single arm study, conducted in infants with Type 1 SMA. The study consisted of a dose-finding Part 1 and a confirmatory Part 2. Part 2 was considered the pivotal trial for SMA Type 1. FIREFISH Part 2 achieved the primary

outcome where 29.3% of infants (12 out of 41 infants) were able to sit without support after 12 months on treatment. This proportion was significantly higher than the pre-defined performance criterion of 5% based on natural history data ($p < 0.0001$). Of the reported secondary outcomes (at 12 months of treatment), 56.1% of infants (23 out of 41 infants) had a CHOP INTEND score of 40 or higher ($p < 0.0001$), 90.2% (37 out of 41 infants) had achieved an increase of at least 4 points in the CHOP INTEND score from baseline ($p < 0.0001$) and 78.0% (32 out of 41 infants) were considered motor milestone responders assessed through the HINE Section 2. At month 12, 85.4% of patients were alive and did not require permanent ventilation (35 out of 41 infants). These efficacy outcomes were consistent with the exploratory efficacy results at month 12 of treatment in FIREFISH Part 1.

SMA Type 2/3

SUNFISH Part 2 (N = 180) was adouble-blind, placebo-controlled, phase III trial that investigated the efficacy and safety of risdiplam after 12 months of treatment in patients with SMA Type 2 or non-ambulatory patients with SMA Type 3 and who were 2 to 25 years of age inclusive. SUNFISH Part 2 achieved its primary end point where patients who received risdiplam had a mean difference versus placebo of 1.55 points (95% confidence interval [CI], 0.30 to 2.81; $p = 0.0156$) in the change of the MFM-32 score from baseline. The first secondary outcome tested (within the statistical testing hierarchy) after the primary outcome was the MFM-32 responders (change of 3 points or more from baseline). This outcome showed that 38.3% of patients in the risdiplam arm (44 out of 115 patients) were considered responders, compared to 23.7% in the placebo group (14 out of 59 patients) with an odds ratio (OR) of 2.35 (95% CI, 1.01 to 5.44; $p = 0.0469$) for risdiplam versus placebo. Subsequently, the change in RULM score was tested, with a mean difference versus placebo of 1.59 points (95% CI, 0.55 to 2.62; $p = 0.0028$). Subsequently, 2 co-outcomes were tested: change from baseline in the total score of HFMSE, which failed to achieve statistical significance (mean difference = 0.58 points; 95% CI, –0.53 to 1.69; $p = 0.3015$) and change from baseline in best percentage predicted value FVC (mean difference = –2.05; 95% CI, –6.67 to 2.56; $p = 0.3804$).

Comparative effectiveness

In SMA Type 1, nusinersen (ENDEAR trial), onasemnogene abeparovec (STR1VE-US trial) and BSC were considered relevant comparators. Relative treatment effects in SMA Type 1 were derived from unanchored indirect treatment comparisons (ITCs). Unanchored comparisons are problematic due to the loss of randomisation and therefore produces results that are likely subject to bias. Results from the Applicant's ITC for patients with SMA Type 1 suggested that risdiplam was more effective for motor function outcomes such as sitting, with the exception of standing, where nusinersen was more effective. The output of the ITC also indicated that risdiplam demonstrated greater prolonged ventilation-free survival and overall survival compared to nusinersen. For the comparison with OA in SMA Type 1, the ITC suggested comparable efficacy of risdiplam and onasemnogene abeparovec in terms of ventilation free survival and mixed results for motor function outcomes with wide interval estimates. For the comparison with BSC, risdiplam was suggested to be more effective for most key outcomes.

Results from the unanchored ITC are highly uncertain as there was limited overlap between study populations. Therefore benefit cannot be concluded over nusinersen or onasemnogene abeparovec in SMA Type 1.

In SMA Type 2 and 3, nusinersen (CHERISH trial) and BSC were considered the relevant comparators. For SMA Type 2 and 3 the Applicant's ITC (ridisplam versus nusinersen) indicated greater effectiveness with ridisplam for motor function using the RULM outcome, but results for the HMFSE outcome were not consistent. Heterogeneity between trial populations was even more evident in this analysis, thereby further limiting the claim of greater benefit. Therefore benefit of risdiplam over nusinersen could not be concluded from the ITC in SMA Type 2 and 3.

2. Safety

In FIREFISH Part 2, at least one adverse event (AE) was reported in all enroled infants. Upper respiratory tract infection was the most commonly reported AE (46.3%), followed by pneumonia (39.0%), pyrexia (39.0%), and constipation (19.5%). Serious AEs (SAEs) were reported in 58.5% (24 out of 41 infants); the majority of SAEs were respiratory related.

Three infants died during the study; two deaths were attributed to pneumonia and one to respiratory failure. In SUNFISH Part 2, at least one AE was reported in 92.5% and 91.7% of enroled patients in the risdiplam and placebo arms, respectively. Upper respiratory tract infection was most commonly reported AE (31.7% and 30.0% of the respective arms), followed by nasopharyngitis (25.8% and 25.0% respectively), pyrexia (20.8% and 16.7% respectively), and headache (20.0% and 16.7% respectively). SAEs were reported in 20.0% and 18.3% of the respective arms. Most SAEs were respiratory related.
Interim analysis was also presented from the JEWELFISH study; an open label single arm study designed to investigate the safety, tolerability and pharmacokinetics/pharmacodynamics of risdiplam in adults, children and infants with SMA. All eligible patients were pre-treated with nusinersen, onasemnogene abeparovec, olesoxime, or investigational product R06885247. The 12 month (interim) data-cut demonstrated that risdiplam was well tolerated in patients with previous exposure to disease modifying treatments for SMA. The most common AEs were upper respiratory tract infections, nasopharyngitis, pyrexia and headache. No treatment related safety findings led to withdrawal from treatment and the overall AE profile was consistent with that of treatment naïve patients in the FIREFISH and SUNFISH trials. There was a 5% rate of discontinuation at this data cut.

3. Cost effectiveness

Separate Markov models with monthly cycles were constructed in Microsoft Excel® for (i) SMA Type 1 and (ii) SMA Type 2 and 3. Both models simulated the progression or regression associated with SMA through a series of motor milestones.

For both the SMA Type 1 and SMA Type 2 and 3 models, direct treatment effects on motor milestones (transitions between motor function health states) and overall survival were modelled. Treatment effects on motor function also imply an indirect treatment effect on overall survival because patients in health states with improved motor function are assumed to have improved survival. It is assumed that attainment of either standing or walking motor milestones are associated with improvements in life expectancy. The Applicant also incorporated treatment effects for respiratory support and bulbar impairment (feeding

support) outcomes and scoliosis. The data sources used to inform health outcomes for the Type 1 model and Type 2 and 3 model are summarised in Table 1 and 2 respectively. Health outcomes and adverse events were informed by key trials and literature identified via the systematic literature review.

Health state utility values in the SMA Type I model were obtained from Malone et al (2019). Health state utility values in the SMA Type 2 and 3 model were generated from a mixed model repeated measures (MMRM) analysis of EQ-5D-5L (which were subsequently converted to 3L via the Van Hout algorithm) data from the SUNFISH trial. While the utility values used by the Applicant are distinctly different from those used in previous HTAs of drugs indicated for SMA, the Review Group notes that measuring robust utility values in infants and young children is challenging. Health state costs were based on a UK burden of illness study conducted by the Applicant.

The Review Group identified a number of issues with the Applicant's model, not limited to; the submitted model was based on patient achievement of motor function milestones, therefore did not encompass all key changes in a patient's quality of life with SMA. Additionally, while patients in the model could experience regression in motor function, patients were just as likely to experience gains in motor functions as they were before the regression. This was considered to lack face validity. A single model was submitted for both SMA Type 2 and Type 3 which may not be clinically valid. The Review Group note there is limited evidence available on the duration of effect for disease modifying therapies in SMA.

Results in the base case represent the perspective of the Health Service Executive (HSE). A discount rate of 4% was applied.

An incremental analysis of costs and benefits of risdiplam compared to BSC, nusinersen and onasemnogene abeparovec was presented by the Applicant for patients with SMA Type 1, and versus BSC and nusinersen for patients with SMA Type 2 and 3. The results of the Applicant's base case cost-effectiveness results for risdiplam in the SMA Type 1 model and SMA Type 2 and 3 model are presented in Table 1 and 2 respectively.

Table 1 Results of Applicant's corrected* base case cost-effectiveness analysis for patients with Type 1 SMA

	Total Costs (€)	Total QALYs	Incremental Costs (€)	Incremental QALYs	ICER (€ per QALY)
Risdiplam	4,814,569	9.71	-	-	-
BSC	472,701	2.43	4,341,868	7.28	596,547
Nusinersen	3,422,009	7.98	1,392,560	1.73	806,307
OA	3,091,817	9.48	1,722,753	0.24	7,326,448

Abbreviations: ICER: incremental cost-effectiveness ratio; **QALY:** quality-adjusted life year; **BSC**: best supportive care **OA** Onasemnogene abeparovec

Incremental results are presented for ridisplam versus comparators. Figures in the table are rounded, and so calculations may not be directly replicable. Analyses are at list prices. * The Review Group corrected the cost applied for OA in the Applicant's base case.

Table 2 Results of Applicant's base case cost-effectiveness analysis for patients with Type 2 and 3 SMA

	Total Costs (€)	Total QALYs	Incremental Costs (€)	Incremental QALYs	ICER (€ per QALY)
Risdiplam	5,602,712	0.27	-	-	-
BSC	1,657,143	-0.47	3,945,569	0.74	5,339,479
Nusinersen	5,307,779	0.11	294,933	0.16	1,829,157

Abbreviations: ICER: incremental cost-effectiveness ratio; **QALY:** quality-adjusted life year; **BSC**: best supportive care

Incremental results are presented for ridisplam versus comparators. Figures in the table are rounded, and so calculations may not be directly replicable. Analyses are at list prices.

The Review Group noted substantially higher utility values for motor function health states were used by the Applicant in the Type 1 model than for similarly defined motor function health states in the Type 2 and 3 model. This lacks face validity given that SMA Type 1 would generally be considered a more severe form of SMA. Also, the Review Group noted the negative QALY gain for BSC in the Type 2 and 3 model and considered that this lacked face validity.

A probabilistic sensitivity analysis (PSA) was conducted by the Applicant, however the Review Group noted that it inappropriately excluded a number of model parameters in the Type 1 model. The results of the Applicant's probabilistic sensitivity analyses for risdiplam in the Type 1 SMA model and Type 2 and 3 SMA model are presented in Table 3 and 4 respectively.

Table 3 Results of Applicant's probabilistic sensitivity analysis for patients with SMA Type 1

	Incremental Costs (€)	Incremental QALYs	ICER (€ per QALY)	Probability (%) ridisplam cost-effective at	
				€45,000	€20,000
Risdiplam	-	-		-	-
BSC	5,938,526	6.50	913,915	6.1	6.0
Nusinersen	1,563,636	1.94	805,201	21.4	21.2
OA	1,166,859	0.19	6,260,233	10.2	10.2

Abbreviations: ICER: incremental cost-effectiveness ratio; **QALY:** quality-adjusted life year; **BSC**: best supportive care **OA** Onasemnogene abeparovec

Incremental results are presented for ridisplam versus comparators. Figures in the table are rounded, and so calculations may not be directly replicable. Analyses are at list prices. Corrected cost applied for OA.

Table 4 Results of Applicant's probabilistic sensitivity analysis for patients with SMA Type 2/3

	Incremental Costs (€)	Incremental QALYs	ICER (€ per QALY)	Probability (%) ridisplam cost-effective at	
				€45,000	€20,000
Risdiplam	-	-	-	-	-
BSC	2,101,503	0.59	3,562,520	11.7	11.6
Nusinersen	323,329	-0.112	Risdiplam is dominated	13.0	13.3

Abbreviations: ICER: incremental cost-effectiveness ratio; **QALY:** quality-adjusted life year; **BSC**: best supportive care

Incremental results are presented for ridisplam versus comparators. Figures in the table are rounded, and so calculations may not be directly replicable. Analyses are at list prices.

A number of scenario analyses were conducted by the Review Group in both models, and the ICERs remained over €500,000/QALY.

4. Budget impact

A budget impact analysis was submitted based on the assumption of an eligible patient population for year 1 of 71 patients, increasing to 91 patients by year 5. The price to wholesaler 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.

5. Patient Organisation Submissions

A Patient Organisation Submission was received from SMA Ireland. It will be provided to the HSE and form part of the data that the HSE considers.

6. Conclusion

The NCPE recommends that risdiplam not be considered for reimbursement until cost-effectiveness can be improved relative to existing treatments*.

**This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.*