6.04 RISDIPLAM, Powder for oral solution 750 micrograms per mL, 80 mL, Evrysdi®, Roche Products Pty Ltd.

1 Purpose of submission

1.1 The Category 2 submission requested Section 100 (Highly Specialised Drugs Program) Authority Required (Written) listing for the treatment of patients with confirmed genetic diagnosis of spinal muscular atrophy (SMA) (*SMN1* deletion or mutation) who have a *SMN2* gene copy number of three.

1.2 Listing was requested on the basis of a cost-minimisation approach (CMA) versus nusinersen. Table 1 provides a summary of the key components of the submission.

Table 1: Key components of the clinical issue addressed by the submission (as stated in the submission)

Component	Description
Population	Patients with confirmed genetic diagnosis of SMA (*SMN1* deletion or mutation) who have an *SMN2* gene copy number of 3 [a]
Intervention	Risdiplam solution administered orally as chronic treatment [b]
Comparator	Nusinersen solution for injection administered intrathecally as chronic treatment
Outcomes	Event free survival Overall survival Individual motor milestone scores and achievements as measured by the HINE-2 and CHOP-INTEND
Clinical claim	In pre-symptomatic SMA patients with genetically confirmed *SMN1* deletion or mutation and a *SMN2* gene copy number of 3, risdiplam is non-inferior in terms of efficacy and safety compared with nusinersen. Risdiplam also has a favourable safety profile in some patients due to a less invasive administration method (oral vs intrathecal).

CHOP-INTEND = Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HINE-2 = Hammersmith Infant Neuromuscular Examination Module 2; SMA = spinal muscular dystrophy; SMN = survival motor neuron

[a] The submission presented data consistent with Population 3 (pre-symptomatic SMA patients with 3 copies of the *SMN2* gene) in the March 2023 risdiplam PBAC submission, however this population subgroup was withdrawn from consideration in March 2023.

[b] Risdiplam dosage dependent on age and weight, with a maximum daily dose of 5 mg.

Source: Table 1.1, p3 of the submission

2 Background

Registration status

2.1 Risdiplam was initially registered by the TGA on the 2 June 2021 'for the treatment of 5q SMA in patients aged 2 months and older'. The indication was amended on 19 May 2023 to remove the age restriction.

Previous PBAC consideration

2.2 Risdiplam was recommended for PBS listing for the treatment of SMA Type 1, 2 or 3a in patients aged 18 years or less, based on non-inferiority to nusinersen at the March

2021 PBAC meeting. A listing for patients with SMA Type 3b was not recommended by the PBAC at this time, however the SMA Type 3b and 3c sub-population was PBS-listed as a result of a flow on of the positive recommendation for a subsequent nusinersen PBAC submission (paragraph 7.23, nusinersen Public Summary Document (PSD), July 2021 PBAC meeting).

2.3 Risdiplam was recommended for PBS listing for the treatment of pre-symptomatic patients with a confirmed genetic diagnosis of SMA who have an *SMN2* gene copy number of one or two at the March 2023 PBAC meeting. The sponsor also initially requested PBS-listing of risdiplam for patients with SMA and an *SMN2* gene copy number of three, but this population subgroup was withdrawn prior to PBAC consideration as the nominated near market comparator onasemnogene abeparvovec (ONA) was not recommended for funding at the November 2022 PBAC meeting.

3 Requested listing

MEDICINAL PRODUCT medicinal product pack	Dispensed Price for Max. Qty	Max. qty units	№.of Rpts	Available brands
Risdiplam 60mg, powder for oral solution	$10,890.26 private published price [a] $10,841.89 public published price	1 bottle	0	Evrysdi

[a] Includes $8.37 ready prepared fee and $40.00 pharmacy mark-up;
Source: Table 1.9of the submission

Category / Program: Section 100
Prescriber type ☒Medical Practitioners
Restriction type: ☒Authority Required – In Writing
Condition: Spinal Muscular Atrophy (SMA)
Treatment Phase: Initial
Treatment criteria:
Must be treated by a specialist medical practitioner experienced in the diagnosis and management of SMA associated with a neuromuscular clinic of a recognised hospital in the management of SMA; or in consultation with a specialist medical practitioner experienced in the diagnosis and management of SMA associated with a neuromuscular clinic of a recognised hospital in the management of SMA. AND Patient must be undergoing initial PBS-subsidised treatment with this drug for untreated disease; OR Patient must be undergoing initial PBS-subsidised treatment, but the patient has initiated treatment via non-PBS supply (e.g. clinical trial, sponsor compassionate access)
Clinical criteria:

The condition must have genetic confirmation of 5q homozygous deletion of the survival motor neuron 1 (*SMN1*) gene; OR The condition must have genetic confirmation of deletion of one copy of the *SMN1* gene in addition to a pathogenic/likely pathogenic variant in the remaining single copy of the *SMN1* gene, AND The condition must be pre-symptomatic SMA, with genetic confirmation that there are 1 to 2 copies of the survival motor neuron 2 (*SMN2*) gene; [a] OR <u>The condition must be pre-symptomatic SMA, with genetic confirmation that there are 3 copies of the survival motor neuron 2 (*SMN2*) gene;</u> AND The condition must be pre-symptomatic; AND The treatment must be given concomitantly with best supportive care for this condition; AND Patient must be untreated with gene therapy.
Population criteria:
Patient must be aged under 36 months prior to commencing treatment.
Prescribing Instructions: Application for authorisation of initial treatment must be in writing (lodged via postal service or electronic upload) and must include: (a) a completed authority prescription form; and (b) a completed spinal muscular atrophy PBS Authority Application Form which includes the following: (i) confirmation of genetic diagnosis of SMA; and (ii) a copy of the results substantiating the number of *SMN2* gene copies determined by quantitative polymerase chain reaction (qPCR) or multiple ligation dependent probe amplification (MLPA)
Administrative Advice: No increase in the maximum number of repeats may be authorised. No increase in the maximum quantity or number of units may be authorised. The approved Product Information recommended dosing is as follows: (i) 16 days to less than 2 months of age: 0.15 mg/kg (ii) 2 months to less than 2 years of age: 0.20 mg/kg (iii) 2 years of age and older weighing less than 20 kg: 0.25 mg/kg (iv) 2 years of age and older weighing 20 kg or more: 5 mg In this authority application, state which of (i) to (iv) above applies to the patient. Based on (i) to (iv), prescribe up to: 1 unit where (i) applies; 2 units where (ii) applies; 3 units where (iii) applies; 3 units where (iv) applies.

Note: <u>Underlined</u> text refers to proposed amendment of the currently listed risdiplam pre-symptomatic PBS restriction.

[a] The term "pre-symptomatic SMA" is not included in this sentence of the current risdiplam pre-symptomatic listing but is included separately as a subsequent clinical criteria (as also included above).

Source: Table 1.10of the submission

3.1 The submission did not propose an effective price for risdiplam and stated that the effective price for nusinersen for the pre-symptomatic treatment of patients with three *SMN2* gene copies (to which risdiplam was cost-minimised) would not be disclosed to the sponsor until a positive recommendation has occurred for risdiplam in this population and upon the sponsor signing a Deed of Confidentiality. Therefore, the sponsor lodged the submission on the basis of an in-principle agreement that the effective price for risdiplam will be no higher than the cost-minimised effective price for the main comparator, nusinersen.

3.2 The submission proposed a change to the existing restriction for initial treatment of pre-symptomatic patients with 1-2 copies *SMN2* to include patients with 3 copies *SMN2.* The submission did not specifically detail a continuation restriction, noting that the current continuation restriction (with an expansion of the treatment phase to include patients with 1-3 copies *SMN2* would be appropriate for patients initiated on risdiplam under this restriction. The Secretariat noted that listings for nusinersen and onasemnogene abeparvovec in patients with pre-symptomatic SMA with 3 copies of the *SMN2* gene are separate PBS item codes from the listings for patients with 1-2 copies. The PBAC considered this approach would also be reasonable for the proposed risdiplam listings for patients with 3 copies of the *SMN2* gene.

3.3 The submission did not propose a specific grandfathering restriction but included treatment criteria to include patients undergoing initial PBS-subsidised treatment who initiated treatment via non-PBS supply (e.g. clinical trial, sponsor compassionate access). The submission reported that eight pre-symptomatic Australian SMA patients, including six patients with three copies of *SMN2*, are currently accessing risdiplam as part of the RAINBOWFISH study. These six patients would be eligible for PBS-listed risdiplam under the proposed listing. However, these patients were not considered in the submission's financial estimates, which may be inappropriate.

For more detail on PBAC's view, see section 7 PBAC outcome.

4 Population and disease

4.1 SMA is an autosomal recessive progressive neuromuscular disease that causes progressive atrophy of skeletal muscles, generalised weakness and disease-related complications that can impact survival. It is caused by the deletion, conversion and/or mutation of the *SMN1* gene on chromosome 5q13, resulting in insufficient levels of functional SMN protein. The SMN gene is duplicated in humans to give rise to a second SMN gene, *SMN2*. Although only 10–20% of the *SMN2* gene protein is fully functional, increased genomic copies of *SMN2* inversely correlates with disease severity among individuals with SMA i.e. patients with milder forms of SMA have higher copy numbers than patients with severe SMA. Consequently, SMA presents across a broad clinical spectrum, ranging from extremely weak infants with a historically dismal prognosis, to more mildly affected, ambulatory children and adults.

4.2 The submission presented an overview of SMA clinical classification (Table 2). This provided a more simplified description of the typical *SMN2* copy number for each SMA type compared to details previously considered by the PBAC (paragraph 4.2, risdiplam PSD, March 2023 PBAC meeting and paragraph 4.1, nusinersen PSD, July 2023 PBAC meeting). Notably, the table below states that patients with SMA Type 2 typically have an *SMN2* copy number of three whereas previous descriptions stated that patients with an *SMN2* copy number of three were commonly classified as having either SMA Type 2 or 3 (3a or 3b).

Table 2: SMA clinical classification according to onset, achieved milestones, evolution and *SMN2* genotype [a]

SMA Type without access to treatment	Age at symptom onset	Able to sit	Able to stand	Able to walk	Typical symptoms	Life expectancy	Typical *SMN2* copy number [c]
0	Prenatal	X	X	X	Severe hypotonia [b]	Death in weeks	1
1	< 6 months	X	X	X	Respiratory failure	Death by 2 years	2
2	6-18 months	✓	X	X	Respiratory complications, wheelchair bound	10—40 years	3
3a	18 months – 3 years	✓	✓	Assisted	Early loss of ambulation	Normal	4
3b	>3 years	✓	✓	Assisted	Later loss of ambulation		
4	>18 years	✓	✓	✓	Slow, progressive muscle weakness. Ambulant until later in life.	Normal	5

SMA = spinal muscular dystrophy; SMN = survival motor neuron

[a] The submission did not provide a validated reference to support this data.

[b] Need for respiratory support at birth; contractures at birth; reduced foetal movements. These patients will present with symptoms of SMA at birth and will be ineligible for pre-symptomatic treatment.

[c] *SMN2* copies in the genome varies between 0 and 8.

Source: Table 1.2, of the submission

4.3 The submission claimed that prior to the availability of disease modifying treatments (DMTs), SMA was classified into clinical subtypes based on age of onset and disease severity. While the introduction of DMTs was not directly linked to the classification of SMA subtypes, use of DMTs generally changes the course of a patient's disease and SMA classification was previously based on the symptoms a patient would experience without treatment. The submission considered that for older patients the clinical subtypes based on age and SMA symptom severity still hold relevance, however for pre-symptomatically diagnosed and treatment-initiated patients, these subtypes are no longer appropriate and instead only represent the natural disease course without access to treatment. However, knowing the natural disease course is important to establish the clinical benefit of pre-symptomatic treatment.

4.4 The submission claimed that the introduction of newborn bloodspot screening (NBS) for SMA in Australia, means that patients can be diagnosed pre-symptomatically. Based on their *SMN2* gene copy number, treatment can then be initiated prior to symptoms developing. The PBAC have previously acknowledged that NBS programs for SMA will soon be introduced across Australia (paragraph 7.3, nusinersen PSD, July 2023 PBAC meeting). The Department of Health and Aged Care NBS website currently lists SMA under "Conditions screened in Australia's NBS programs".

For more detail on PBAC's view, see section 7 PBAC outcome.

5 Comparator

5.1 While the submission noted that both nusinersen and ONA were recommended for funding for the treatment of pre-symptomatic SMA patients with three *SMN2* gene copies by the PBAC in July 2023 and that both nusinersen and ONA are currently PBS listed for this indication, the submission nominated only nusinersen as the main comparator to risdiplam. Nusinersen was considered to be an appropriate comparator to risdiplam; however, it is likely that some families will consider both risdiplam and ONA as potential SMA treatments and risdiplam could be used instead of ONA in some patients. Therefore, ONA would also be a reasonable comparator for risdiplam.

5.2 The submission claimed that clinical insight collected for the submission indicated that when faced with a choice between treatment with risdiplam, nusinersen and ONA, a preference exists among families for one-time treatment with ONA. The submission claimed that while the majority of newborn patients are expected to be treated with ONA there are several situations in which ONA will not be chosen, in which case a choice will need to be made between risdiplam and nusinersen. The submission claimed that treatment with ONA may not be feasible in some patients due to high adeno-associated viral vector serotype 9 (AAV9) titres, baseline bloods that indicate abnormal liver function tests or other medical conditions that would compromise safety, or that there can be a family preference to not receive gene therapy (e.g. due to the safety profile and/or the irreversible nature of treatment). The proposed restriction would not restrict the use of risdiplam to patients for whom ONA was unsuitable.

5.3 The proposed clinical algorithm listed risdiplam, nusinersen and ONA as treatment options for pre-symptomatic SMA patients with three copies of *SMN2*. Therefore, the proposed clinical algorithm was consistent with the nomination of nusinersen as comparator, but also highlighted that ONA should also be a comparator for the requested patient population.

5.4 Even though ONA was not a nominated comparator, the submission included supplementary data that presented a clinical comparison of risdiplam with ONA in patients with pre-symptomatic SMA with three *SMN2* gene copies. The submission claimed that risdiplam was non-inferior to ONA in this patient population.

5.5 In the context of the cost-minimisation approach taken by the submission, a further consideration for PBAC is that, under Section 101(3B) of the National Health Act 1953, when the proposed medicine is substantially more costly than an alternative therapy, the committee cannot make a positive recommendation unless it is satisfied that, for some patients, the proposed medicine provides a significant improvement in efficacy and/or reduction of toxicity over the alternative therapy. If the committee is so satisfied, it must make a statement to this effect.

For more detail on PBAC's view, see section 7 PBAC outcome.

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted and welcomed the input from individuals (1), and the National Paediatric Medicines Forum via the Consumer Comments facility on the PBS website. The comments noted the advantages of oral administration and the benefits of avoiding delayed treatment in patients with SMA. The PBAC noted the advice received from the National Paediatric Medicines Forum that the oral route of administration, as opposed to intrathecal or intravenous infusion will assist rural and remote patients access treatment, and that the PBS listing of risdiplam for patients with confirmed genetic diagnosis of SMA who have a *SMN2* gene copy number of three would be likely to improve equitable access and reduce anxiety for SMA families with a recently diagnosed infant.

Clinical studies

6.3 The submission was based on unanchored numerical comparisons using single arm studies to compare risdiplam (RAINBOWFISH) and nusinersen (NURTURE). These trials have previously been considered by the PBAC. The PBAC had previously considered data from RAINBOWFISH for patients with 1-2 copies *SMN2* (clinical cut-off date [CCOD] 1 July 2021; N=18) at the March 2023 PBAC meeting, but the data from RAINBOWFISH presented in the current submission (CCOD 20 February 2023; N=26) included 13 patients with 3 copies *SMN2,* representing a more recent data cut with more patients. While RAINBOWFISH enrolled patients with any number of *SMN2* copies, data for patients with three *SMN2* copies has not previously been considered by the PBAC as this subpopulation was withdrawn from consideration prior to the March 2023 PBAC meeting. NURTURE (n=25) was most recently considered at the July 2023 PBAC meeting for nusinersen in pre-symptomatic SMA patients with three *SMN2* gene copies.

6.4 Details of the studies presented in the submission are provided in Table 3.

Table 3: Risdiplam and nusinersen studies and associated reports presented in the submission

Study ID	Protocol title/ Publication title	Publication citation
RAINBOWFISH	Primary CSR Study BN40703, (RAINBOWFISH) An Open-Label Study Of Risdiplam In Infants With Genetically Diagnosed And Presymptomatic Spinal Muscular Atrophy.	CSR Report No. 1122192. August 2023 (Clinical Appendix)
	Interim CSR Study BN40703, (RAINBOWFISH) An Open-Label Study Of Risdiplam In Infants With Genetically Diagnosed And Presymptomatic Spinal Muscular Atrophy.	CSR Report No. 1109915 2021; October 2021 (Clinical Appendix)
	A Study of Risdiplam in Infants With Genetically Diagnosed and Pre-symptomatic Spinal Muscular Atrophy (Rainbowfish).	https://classic.clinicaltrials.gov/show/NCT03779334
	Finkel. Preliminary Efficacy and Safety Data in Risdiplam-Treated Infants with Pre-symptomatic SMA.	Neurology. 2022; 98
	Servais. Preliminary Efficacy and Safety Data in Risdiplam-Treated Infants with Pre-symptomatic Spinal Muscular Atrophy.	J Neuromuscul Dis. 2022; 9: S114-S115
	Servais. A study of risdiplam in infants with pre-symptomatic spinal muscular atrophy (SMA).	Dev Med Child Neurol. 2022;64: 71
NURTURE	Crawford. Continued benefit of nusinersen initiated in the presymptomatic stage of spinal muscular atrophy: 5-year update of the NURTURE study	Muscle Nerve. 2023;68(2):157-170
	De Vivo. Nusinersen initiated in infants during the presymptomatic stage of spinal muscular atrophy: Interim efficacy and safety results from the Phase 2 NURTURE study	Neuromuscul Disord. 2019;29(11):842-56
	A Study of Multiple Doses of Nusinersen (ISIS 396443) Delivered to Infants With Genetically Diagnosed and Presymptomatic Spinal Muscular Atrophy.	https://classic.clinicaltrials.gov/show/NCT02386553
	Kirschner. Impact of Nusinersen on Caregiver Experience and HRQoL in Pre-symptomatic SMA: NURTURE Study Results.	J Neuromuscul Dis. 2022;9: S113-S114

Blue shading indicates items presented in the March 2023 submission, which was considered by the ESC, but data for the subpopulation of patients with SMA with 3 copies of *SMN2* was subsequently withdrawn prior to PBAC consideration.
Source: Table 2.4of the submission

6.5 The key features of the included studies are summarised in Table 4.

Table 4: Key features of the included evidence

Study, n	Design/duration	Bias	Treatment	Population	Outcomes
RAINBOWFISH N=26 [a, b]	MC, NC, OL, median (range) treated for 20.44 (10.6-41.9) months	High	Risdiplam once daily, oral target dose	Pre-symptomatic SMA patients ≥ 2 copies of *SMN2* aged ≤ 6 weeks	Primary: proportion of patients sitting without support after 12 months of treatment [c] Other: OS, EFS, HINE-2, CHOP-INTEND, safety
NURTURE N=25 [d]	MC, NC, OL, 5 years	High	Nusinersen IC 12 mg; loading doses (Days 1, 15, 29 and 64) then every 4 months	Pre-symptomatic patients with 2 or 3 copies of *SMN2,* aged ≤ 6 weeks	Primary: time to death or respiratory intervention [e] Other: OS, EFS, HINE-2, WHO milestones, CHOP-INTEND, safety

CHOP-INTEND = The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; EFS = event-free survival (survival without permanent ventilation); HINE-2 = Hammersmith Infant Neurological Examination Module 2; IC = intrathecal; MC = multi-centre; NC = non-comparative single arm study; OL = open label; OS = overall survival; SMA = spinal muscular atrophy; WHO = World Health Organisation
Blue shading indicates data previous considered by the PBAC.
a RAINBOWFISH included 13 patients with an *SMN2* copy number of 3.
b RAINBOWFISH was presented in the March 2023 risdiplam submission, however only data for the subpopulation of patients with SMA with a *SMN2* gene copy number of 1 or 2 was considered by the PBAC. At this time RAINBOWFISH results included a total of 18 patients.
c Defined as "sitting without support for 5 seconds" as assessed in Item 22 of the BSID-II Gross Motor Scale. The primary efficacy analysis population was defined as all patients in the ITT population with two *SMN2* copies (excluding the known *SMN2* gene modifier mutation c.859G > C) and a baseline CMAP amplitude ≥ 1.5 mV and is therefore a subset of the ITT population.
d NURTURE included 10 patients with an *SMN2* copy number of 3.
e Intervention defined as invasive or non-invasive for ≥6 hours/day continuously for ≥7 days or tracheostomy.
Source: Table 2.5 of the submission

6.6 In both RAINBOWFISH and NURTURE, patients with SMA with an *SMN2* copy number of three were a subpopulation of all enrolled patients. RAINBOWFISH enrolled 13 patients (13/26 patients = 50%) and NURTURE enrolled 10 patients (10/25 patients = 40%) with three copies of *SMN2*.

6.7 Compound muscle action potential (CMAP) amplitude is used for tracking disease progression in SMA with a higher measure reflecting a higher motor functioning status. The mean baseline CMAP amplitude in RAINBOWFISH (3.66 mV) was higher than in NURTURE (2.87 mV). The submission proposed that this was likely owing to the fact that patients with four *SMN2* gene copies were included in the RAINBOWFISH study; however, when comparing CMAP specifically in patients with three *SMN2* copies, the mean CMAP amplitude at baseline in RAINBOWFISH (4.42 mV) remained higher than NURTURE (3.11 mV). The evaluation and the ESC considered it was likely that patients enrolled in NURTURE had a lower motor functioning status at baseline than the patients in RAINBOWFISH and motor function outcomes may be biased in favour of risdiplam.

6.8 The submission did not nominate a minimal clinically important difference or any non-inferiority margins for any outcome for patients with SMA or specifically for paediatric patients with pre-symptomatic SMA. The submission claimed that given the lack of comparative studies, and rare nature of SMA (hence the very small trial populations), there was an inherent lack of precision in the confidence estimates for the naïve comparisons presented in this submission and that therefore it was not appropriate to assess non-inferiority by applying the lower limit of reported hazard ratios/mean

differences thresholds. While this may be reasonable, it highlighted the high uncertainty associated with the evidence presented in the submission.

Comparative effectiveness

6.9 Due to the lack of direct comparative trials of risdiplam versus nusinersen, or trials with a common comparator arm, the submission presented numerical comparisons of risdiplam versus nusinersen study data for the treatment of pre-symptomatic SMA patients with an *SMN2* copy number of three. Similarly, an unanchored comparison was presented in the March 2023 risdiplam submission for patients with 1-2 copies of *SMN2*. For pre-symptomatic patients aged <36 months with an *SMN2* gene copy number of 1 or 2 in the March 2023 submission), the ESC previously considered the claim of non-inferior effectiveness was clinically plausible, consistent with previous comparisons between risdiplam and nusinersen. However, the ESC considered this comparison was associated with a notable degree of uncertainty as the quality of evidence was poor and the unanchored comparison carried a substantial risk of bias due to the lack of a common comparator. In its consideration of this population in the March 2023 submission, the ESC also considered the RAINBOWFISH and NURTURE trials both had a high risk of bias given they were single arm studies with no control group and small patient numbers (paragraph 6.52, risdiplam PSD, March 2023 PBAC meeting). As the unanchored indirect comparison presented in the submission was undertaken in the same way and based on the same studies as in the March 2023 risdiplam submission, the evaluation and the ESC considered the results should be interpreted with caution and may not provide accurate information on the magnitude of the incremental benefit of treatment with risdiplam versus nusinersen prior to symptom onset in the proposed population.

6.10 For patients with three *SMN2* gene copies, both RAINBOWFISH (median treatment duration 20.4 months) and NURTURE (median follow-up of 4.9 years) reported no deaths and no patients requiring permanent ventilation. The ESC noted that while neither study reported any deaths or permanent ventilation in SMA patients with three copies of *SMN2*, it was likely that these patients would not have experienced death or permanent ventilation within the follow-up period due to the natural progression of their SMA, even if they hadn't been treated with risdiplam or nusinersen. As such, results for this outcome were of limited usefulness.

6.11 The submission quantitatively compared Hammersmith Infant Neurological Examination Module 2 (HINE-2) total scores for SMA patients with three *SMN2* copies in RAINBOWFISH and NURTURE (Table 5). HINE-2 consists of 8 items developed to assess neurological function for infants (but not specifically for SMA). HINE-2 has a maximum possible score of 26, with a score of 0 indicating inability to perform a task. The PBAC previously considered the outcome of HINE-2 for risdiplam at the March 2021 and March 2023 PBAC meetings.

Table 5: HINE-2 total score RAINBOWFISH vs NURTURE in patients with 3 *SMN2* gene copies

		Risdiplam (N=13)	Nusinersen (N=10)	Observed difference	Estimated difference (95% CI) [c]	P value [c, d]
Baseline mean HINE-2		3.00 (1.41)	3.2 (1.87)	-0.2	0.78 (-11.48 – 13.04)	0.87
Mean change in HINE-2 from baseline (SD)	Week 8 / 64 days [a]	2.46 (1.90)	2.2 (2.66)	0.26	0.83 (-11.40 – 13.07)	0.86
	Week 28 / 183 days [a]	13.83 (3.56) [b]	13.4 (3.10)	0.43	0.97 (-11.19 – 13.13)	0.84
	Week 40 / 302 days [a]	19.17 (2.08) [b]	19.5 (1.96)	-0.33	0.60 (-19.08– 20.27)	0.94
	Week 52 / 365 days [a]	21.92 (2.10)	21.2 (2.15)	0.72	1.22 (-20.88 – 23.33)	0.89

HINE-2 = Hammersmith Infant Neurological Examination Module 2; SD = standard deviation; SMN = survival of motor neuron

[a] The RAINBOWFISH assessment schedule differs to NURTURE. The RAINBOWFISH assessment schedules are in weeks and NURTURE days.

[b] n=12

[c] This data could not be independently verified during the evaluation and the source of these values was unclear.

[d] The two-sample t-test was purely exploratory and was only performed on the absolute mean value at each time point, and so does not account for any differences in the studies (including baseline score). An assumption was made that the populations were normally distributed.

Source: Table 2.23 of the submission

6.12 An exploratory two-sample t-test was performed to test the null hypothesis which found there was no statistically significant ($p < 0.05$) difference between absolute mean values at any time point for the HINE-2 for RAINBOWFISH vs NURTURE patients with three *SMN2* gene copies. At all reported timepoints there did not appear to be any substantial difference between the results for risdiplam and nusinersen.

6.13 The submission presented a summary of HINE-2 motor milestones by visit for RAINBOWFISH vs NURTURE in patients with three *SMN2* gene copies (Table 6). The evaluation and the ESC considered that when accounting for the different assessment schedules, there appeared to be no considerable differences observed in the achievement of HINE-2 motor milestones up to week 52.

Table 6: Summary of improvement in HINE-2 motor milestones in patients with 3 *SMN2* gene copies

	RIS	NUSI	RIS	NUSI	RIS	NUSI	RIS	NUSI	RIS	NUSI
Improvement in HINE-2, N (%)	**Week 0**	**Week 0**	**Week 16**	**Day 64**	**Week 28**	**Day 183**	**Week 40**	**Day 302**	**Week 52**	**Day 365**
N	13	10	13	10	13	10	12	10	13	10
Head control: all time upright	1 (7.7)	2 (20)	11 (84.6)	5 (50)	11 (84.6)	10 (100)	12 (100)	10 (100)	13 (100)	10 (100)
Ability to kick, touch toes	0	0	3 (23.1)	0	8 (61.5)	7 (70)	12 (100)	9 (90)	13 (100)	9 (90)
Rolling, Prone to supine or supine to prone	1 (7.7)	0	7 (53.8)	1 (10)	12 (92.3)	9 (90)	12 (100)	10 (100)	13 (100)	9 (90)
Sitting, stable	0	0	0	0	9 (69.2)	5 (50)	12 (100)	10 (100)	13 (100)	10 (100)
Crawling, on hands and knees	0	0	0	0	2 (15.4)	1 (10)	10 (83.3)	8 (80)	13 (100)	9 (90)
Stands unaided	0	0	0	0	0	0	0	1 (10)	10 (76.9)	7 (70)
Cruising (walk holding on)	0	0	0	0	0	1 (10)	5 (41.7)	7 (70)	12 (92.3)	10 (100)
Walking independently	0	0	0	0	0	0	0	0	9 (69.2)	5 (50)

HINE-2 = Hammersmith Infant Neurological Examination Module 2; NUSI = nusinersen; RIS = risdiplam; SMN = survival of motor neuron
Note: NURTURE assessment schedule differs to RAINBOWFISH and hence results are grouped according to closest assessment schedule time point.
Blue shading indicates data previously presented in the July 2023 nusinersen submission.
Source: Table 2.25 of the submission.

6.14 The submission quantitatively compared the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) total scores for RAINBOWFISH and NURTURE (Table 7). CHOP-INTEND is a measure of motor function that was developed to evaluate both active and elicited reflex movement such as spontaneous movement of upper and lower extremity, hand grasping, rolling, head control, and others. It consists of 16 items, each assessing a specific motor task, with a total score range of 0 to 61, with higher scores consistent with better motor function. The PBAC previously considered the outcome of CHOP-INTEND for risdiplam at the March 2021 and March 2023 PBAC meetings.

Table 7: CHOP-INTEND total score RAINBOWFISH vs. NURTURE in patients with 3 *SMN2* gene copies

		Risdiplam (N=13)	Nusinersen (N=10)	Observed difference	Estimated difference (95% CI) [c]	p-value [c]
Baseline mean CHOP-INTEND		53.77 (5.76)	51.9 (6.10)	1.87	1.51 (-56.61 – 59.63)	0.95
Mean change in CHOP-INTEND from baseline (SD):	Week 8 / 64 days [a]	4.38 (6.45)	5.4 (5.21)	-1.02	1.07 (-7.34 – 9.49)	0.74
	Week 28 / 183 days [a]	9.33 [b] (5.50)	8.9 (5.32)	0.43	0.87 (-5.67 – 7.41)	0.73
	Week 40 / 302 days [a]	9.85 (5.98)	9.9 (4.04)	-0.05	1.63 (-6.22 – 9.48)	0.60
	Week 52 / 365 days [a]	9.92 (5.62)	10.5 (5.74)	-0.58	0.77 (-6.51 – 8.04)	0.78

CHOP INTEND = Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CI = confidence interval; SD = standard deviation; SMN = survival of motor neuron

[a] The RAINBOWFISH assessment schedule differs to NURTURE. The RAINBOWFISH assessment schedule is in weeks and while NURTURE is in days. The two-sample t-test was purely exploratory and was only performed on the absolute mean value at each time point, and so does not account for any differences in the studies (including baseline score). An assumption was made that the populations were normally distributed.

[b] n=12

[c] This data could not be independently verified during the evaluation and the source of these values was unclear

Source: Table 2.24 of the submission

6.15 The submission provided results for the observed difference in mean change in CHOP-INTEND from baseline up to 52 weeks. At all reported time points there did not appear to be a substantial difference between the results for risdiplam and nusinersen.

6.16 For the mean change in HINE-2 total score (Table 5) and mean change in CHOP-INTEND (Table 7) it was not clear what adjustments had been made to calculate the "estimated difference" and why these results differed from the observed values. The Pre-Sub-Committee Response (PSCR) stated the reference to their source (statistical appendix) was an error and that all the relevant information for the two-sample t-test was provided in the submission. The ESC considered it remained unclear how the 95% CIs and p-values were calculated and why the observed versus the estimated values differed. Overall, the evaluation considered that comparisons between RAINBOWFISH and NURTURE were made only on point estimates of change from baseline in HINE-2 scores and CHOP-INTEND scores, and statistical comparisons were likely unreliable given the lack of multiplicity adjustments and the use of subgroups.

Comparative harms

6.17 The submission claimed that in pre-symptomatic SMA patients with a *SMN2* copy number of three, risdiplam is non-inferior in terms of safety compared with nusinersen but also claimed that risdiplam has a favourable safety profile in some patients due to a less invasive administration method (oral for risdiplam and intrathecal for nusinersen).

6.18 The PBAC previously noted that the long-term safety of repeated lumbar puncture associated with nusinersen in the context of a lifelong disease was unknown (paragraph 7.5, nusinersen PSD, July 2019 PBAC meeting). The PBAC had previously

considered that, given the less invasive route of administration of risdiplam compared to nusinersen the conclusion that risdiplam has a favourable safety profile in some patients was reasonable (paragraph 7.8, risdiplam PSD, March 2021 PBAC meeting).

6.19 The submission provided an overview of adverse events (AEs) for all patients in RAINBOWFISH and NURTURE (Table 8). The submission claimed that there was nothing to suggest clinically that the safety profile for pre-symptomatic SMA patients with three *SMN2* copies would be different to the general SMA population. This was likely reasonable.

Table 8: Overview of adverse events in RAINBOWFISH and NURTURE, ITT population

	RAINBOWFISH N=26 n (%)	**NURTURE N=25 n (%)**
Total number of patients with at least one AE	24 (92.3)	25 (100)
Total number of AEs	203	NR
Total number of deaths	0	0
Total number of patients withdrawn from study due to an AE	0	0
Total number of patients with at least one:		
AE with fatal outcome	0	0
Serious AE	4 (15.4)	12 (48)
Serious AE leading to withdrawal from treatment	0	0
Serious AE leading to dose modification/interruption	0	0
Treatment Related Serious AE	0	0
AE possibly related to lumbar puncture procedure	NA	8 (32)
AE leading to withdrawal from treatment	0	0
AE leading to dose modification/interruption	2 (7.7)	NR
Treatment related AE	7 (26.9)	8 (32)
Related AE leading to withdrawal from treatment	0	0
Related AE leading to dose modification/interruption	0	NR
Grade 3-5 AE	5 (19.2%)	17 (68%)

AE = adverse event; NR = not reported

Blue shading indicates data previous considered by PBAC. An earlier data cut of the RAINBOWFISH data was previously considered by the PBAC.

Source: Table 2.21 of the submission

6.20 An overview of AEs in RAINBOWFISH and NURTURE in the subset of patients with three *SMN2* gene copies is provided in Table 9.

Table 9: Overview of adverse events in RAINBOWFISH and NURTURE in patients with 3 *SMN2* gene copies

Outcome, n (%)	RAINBOWFISH 3 *SMN2* N=13 (%)	NURTURE 3 *SMN2* N=10 (%)
Any AE	12 (92.3%)	10 (100)
AE related or possibly related to study treatment	4 (30.8%)	6 (60%)
AE of Grade 3 severity or higher	1 (7.7%)	NR
Serious AE	0	3 (30%)
Severe AE	NR	0
Serious AE related to study treatment	0	0
AE related or possibly related to lumbar puncture	NA	4 (40%) [a]
AE leading to study discontinuation	0	0
AE leading to death	0	0

AE = adverse event; NR= not reported; NA= not applicable; SMN = survival of motor neuron
Note: For each category, patients are included only once, even if they experienced multiple events in that category.
Note 2: AEs were considered treatment related if they were classified by the investigator as possibly, probably, or definitely related to study treatment.
[a] Included 3 patients with events possibly related to lumbar puncture and 1 patient with an event related to lumbar puncture.
Blue shading indicates data previous considered by PBAC at its July 2023 meeting.
Source: Table 2.25 of the submission

6.21 The submission claimed that the safety profile of risdiplam demonstrated a lower rate of serious AEs compared to nusinersen. For RAINBOWFISH this data corresponded to the time when the median treatment exposure was 20.4 months (primary analysis) and for NURTURE there was a median follow-up duration of 4.9 years. Due to the different timeframes involved, the comparison of AEs observed for patients with three copies of *SMN2* enrolled in RAINBOWFISH and NURTURE was of limited usefulness.

6.22 The PBAC previously evaluated NURTURE safety data for patients with SMA with two and three copies of *SMN2* and noted that the majority of adverse events in NURTURE were respiratory in nature and appeared to be related to the SMA disease process (paragraph 6.27, nusinersen PSD, July 2023 PBAC meeting).

Benefits/harms

6.23 A benefits and harms table was not presented as the submission made a claim of non-inferior efficacy and safety for risdiplam versus nusinersen for the pre-symptomatic treatment of patients with three copies of *SMN2*.

Clinical claim

6.24 The submission described risdiplam as non-inferior in terms of effectiveness compared to nusinersen. The evaluation considered that the claim of non-inferior efficacy may be clinically plausible but was not clearly supported by the evidence presented because the quality of evidence was poor, based on small single arm studies with a small subset of patients having 3 copies *SMN2*, and the unanchored comparison carried a substantial risk of bias due to the lack of a common comparator.

6.25 However, in its consideration of risdiplam for pre-symptomatic treatment of patients with 1-2 *SMN2* copies, the PBAC had also considered that despite the poor quality of evidence (small sample size, short follow up and differences in assessment times for

specific outcomes), a clinical claim of non-inferiority between risdiplam and nusinersen was clinically plausible (paragraph 7.6, risdiplam PSD, March 2023 PBAC meeting). The ESC agreed with the evaluation that the clinical claim of non-inferior effectiveness compared with nusinersen for patients with 3 *SMN2* copies was likely to be clinically plausible, consistent with the PBAC's consideration for patients with 1 to 2 copies of *SMN2*.

6.26 Previously, the PBAC noted that although there was no direct comparison of safety between risdiplam versus nusinersen, given the less invasive route of administration of risdiplam compared to nusinersen the PBAC considered that the conclusion that risdiplam has a favourable safety profile in some patients was reasonable (paragraph 7.8, risdiplam PSD, March 2021 PBAC meeting*).* The ESC agreed with the evaluation that the claim of non-inferior safety compared to nusinersen but a favourable safety profile in some patients due to the less invasive route of administration compared to nusinersen, appeared reasonable.

6.27 The PBAC considered that the claim of non-inferior comparative effectiveness compared with nusinersen was reasonable, noting the limitations of the data available.

6.28 The PBAC considered that the claim of non-inferior comparative safety compared to nusinersen was reasonable.

Comparison of risdiplam with onasemnogene abeparvovec (ONA)

6.29 The submission also provided a clinical comparison of risdiplam versus ONA in patients with pre-symptomatic SMA with three *SMN2* copies in a supplementary analysis.

6.30 No direct head-to-head evidence was identified in the submission for the clinical comparison of risdiplam vs ONA in pre-symptomatic SMA patients with three *SMN2* gene copies. In the supplementary literature search, one single arm study was identified that investigated the efficacy and safety of ONA in pre-symptomatic SMA patients (SPR1NT). The details of SPR1NT have previously been reviewed by the PBAC, most recently for the ONA submission in July 2023. The PBAC previously noted that SPR1NT was associated with a high degree of bias (paragraph 6.10, ONA PSD, July 2023 PBAC meeting).

6.31 The evaluation considered the clinical claim of non-inferior efficacy and safety for risdiplam vs ONA may be clinically plausible but was not clearly supported by the evidence presented because:

- Similar to the comparison of risdiplam and nusinersen, the data provided in the submission was an unanchored comparison with a substantial risk of bias. The single arm, open label study used to demonstrate efficacy for ONA in patients with SMA with three copies of *SMN2* also had a high risk of bias.
- Comparisons between risdiplam and ONA were made using point estimates of BSID-III fine and gross motor raw and scaled scores. However, the timepoints at

which data were collected differed between the two studies making comparisons difficult and no formal statistical comparisons were provided.

- The submission provided limited additional safety data to inform the comparison of risdiplam and ONA. Previously, the PBAC found that it was difficult to make an informed conclusion with respect to the safety profile of ONA compared to risdiplam (paragraph 6.28, ONA PSD, July 2023 PBAC meeting).

Economic analysis

6.32 The submission presented a CMA for risdiplam versus nusinersen. The key components and assumptions of the CMA are detailed in Table 10.

Table 10: Key components and assumptions of the cost-minimisation approach

Component	Description
Therapeutic claim: effectiveness	The efficacy of risdiplam was assumed to be non-inferior to nusinersen in pre-symptomatic SMA patients with 3 *SMN2* gene copies. The ESC considered this was clinically plausible but supported by limited evidence.
Therapeutic claim: safety	The safety of risdiplam was assumed to be non-inferior to nusinersen in pre-symptomatic SMA patients with 3 *SMN2* gene copies. The evaluation and the ESC considered this was likely to be reasonable.
Evidence base	The primary clinical claim for pre-symptomatic SMA patients with 3 *SMN2* gene copies was supported by the RAINBOWFISH study for risdiplam and the NURTURE study for nusinersen. Unanchored indirect comparisons of subgroup data from these studies were used to inform the claim of non-inferior effectiveness and safety.
Equi-effective doses	The CMA presented in the submission included a time horizon of 5 years, with calculations incorporating risdiplam dosing dependent on the patient's age and body weight over time (from birth) and nusinersen dosing of 12 mg (5 mL) per intrathecal injection administration with 6 administrations in year 1 and 3 administrations from year 2 onwards. This method of establishing equi-effective doses was inconsistent with the PBAC's recommendation for the March 2023 risdiplam submission that was based on equi-effective doses of 5 mg of risdiplam daily and nusinersen 12 mg (5 mL) per administration every four months (three per year, i.e. excluding nusinersen loading doses) consistent also with its previous advice in patients with SMA type 1-3 (paragraph 7.2, risdiplam PSD, March 2023).
Direct medicine costs	The CMA presented in the submission used weight-based dosing to determine the direct medicine costs for risdiplam. However, the CMA incorporated the published AEMP for risdiplam ($10,841.89 per 60 mg bottle), which was previously determined based on a 5 mg daily dose of risdiplam. The 5 mg dose was assumed to be used by patients once they are ≥2 years of age (and ≥20 kg), from which time the cost per patient per month will remain constant for the remainder of the time a patient is receiving risdiplam. Prior to this, patients use a lower dose of risdiplam. Consequently, as the published AEMP, risdiplam dosing by age/weight and nusinersen dosing including loading doses were all used in the CMA presented in the submission, it resulted in the drug costs per patient being lower for risdiplam than nusinersen.
Other costs or cost offsets	Intrathecal administration costs associated with nusinersen administration ($435.95 per administration based on the sum of fees for MBS items 105, 17610, 21945, 23010 and 18216) were included in the calculations presented in the submission. Nusinersen administration costs were previously not incorporated into the calculation of the risdiplam cost-minimised price (paragraph 6.66, risdiplam PSD, March 2023 PBAC meeting) and it appeared the submission included them to show there would be cost-savings to the MBS associated with the proposed listing.

CMA = cost-minimisation approach; AEMP = approved ex-manufacturer price; SMA = Spinal Muscular Atrophy, SMN =survival motor neuron.
Source: Table 3.1 of the submission.

6.33 The CMA presented in the submission incorporated a risdiplam dosing regimen that was dependent on the patient's age and body weight as per the risdiplam PI. For nusinersen, the CMA assumed that patients received four loading doses in Year 1 followed by one dose every four months.

6.34 The submission used World Health Organisation (WHO) data to estimate the average weight of patients from birth until a body weight of 20 kg is reached. The CMA assumed that patients began treatment when they were aged one month and continued treatment uninterrupted for the five-year duration of the CMA. Patients were therefore assumed to commence risdiplam treatment at a low dose (0.15 mg/kg

for patients aged under two months of age), with the daily dose increasing over time to finally reach a steady state dose of 5 mg when patients were two years of age or over and weighed ≥ 20kg. This correlated to the use of 8.9 bottles of risdiplam in Year 1, 13.3 bottles in Year 2, 19.9 bottles in Year 3, 23.2 bottles in Year 4 and 26.4 bottles in Year 5 per patient. The CMA calculated that on average a child would be expected to reach 20 kgs in weight in their 71st month of life (5.95 years). Therefore, patients did not reach the steady state dose of risdiplam over the five-year duration of the CMA.

6.35 The PSCR noted that the cost minimisation approach in the submission was consistent with the approach proposed in the submission for patients with 1-2 copies SMN2 in March 2023. The PBAC previously considered that the equi-effective doses proposed in the March 2023 risdiplam resubmission were inconsistent with, and less conservative than the previous calculations because:

- Loading doses for nusinersen were included in the calculation of equi-effective doses. This differed to the CMA in the March 2021 risdiplam PBAC submission (for Type 1-3a symptomatic SMA) where price parity was requested to nusinersen maintenance dosing only (i.e., three administrations per year over five years).
- For pre-symptomatic patients with 1-2 copies *SMN2* the equi-effective dose of risdiplam was based on the patient weight and the dose did not reach the maximum 5 mg daily until the patient was aged 5.95 years. The cost of risdiplam after year 6 (when patients would use the maximum 5 mg daily dose) would be much greater than in years 1-5. This differed to the CMA in the March 2021 risdiplam submission which was based on the maximum daily dose for risdiplam (paragraph 6.60, risdiplam PSD, March 2023).

6.36 For the March 2023 risdiplam submission, the PBAC considered the inclusion of loading doses for nusinersen and weight-based dosing for risdiplam were not justified and the PBAC's positive recommendation was based on equi-effective doses of 5 mg of risdiplam daily and nusinersen 12 mg (5 mL) per administration every 4 months (3 per year, i.e. excluding nusinersen loading doses) consistent with its previous (March 2021 PBAC meeting) advice in patients with SMA type 1-3 (paragraph 7.2, risdiplam PSD, March 2023).

6.37 The PSCR noted that the PBAC Guidelines state that the equi-effective dose should be estimated based on the relevant clinical trial data of the proposed population and what is recommended in TGA-approved product information (PBAC Guidelines v5.0, 2016). The PSCR stated that the recommended once daily dose of risdiplam is determined by age and body weight and the method of estimation used reflects the appropriate dose, for the particular age and weight of the population in the TGA-approved product information and was informed by the relevant clinical trial (RAINBOWFISH). However, the PBAC Guidelines (2016 v5.0, Section 3B.2) state, for ongoing medicines, 'steady state' dosing (the average dose after titrations are complete) is generally most relevant. Maintenance dosing (i.e., three administrations

per year) may be considered the relevant nusinersen steady state dosing regimen (paragraph 6.61, risdiplam PSD, March 2023).

6.38 The submission stated that the effective price for nusinersen for pre-symptomatic SMA patients with three gene copies has not yet been disclosed to the sponsor and that the submission was lodged on the basis of an in-principle agreement that the effective price for risdiplam will be no higher than the cost-minimised effective price of nusinersen in this patient population.

6.39 While the CMA presented in the submission incorporated risdiplam dosing based on the patient's age/weight and nusinersen dosing including loading doses in year 1, the risdiplam price used in the CMA ($10,841.89) was the current published AEMP per 60 mg risdiplam bottle, which had previously been determined based on the cost-minimisation of risdiplam and nusinersen drug costs (i.e. equi-effective dose of risdiplam 5 mg/day and nusinersen 12 mg once every 4 months with no loading doses). This resulted in a large cost saving associated with risdiplam compared to nusinersen as presented in the CMA.

6.40 The CMA presented in the submission used risdiplam and nusinersen published drug prices and calculated the number of risdiplam bottles used per patient based on dosing as in the PI. The results of the CMA as proposed in the submission are presented in Table 11.

Table 11: Results of cost-minimisation approach risdiplam versus nusinersen (published drug prices)

	Year 1	Year 2	Year 3	Year 4	Year 5	5 year total
Risdiplam costs						
Total bottles [a]	8.94	13.30	19.91	23.17	26.37	
Price per bottle [b]	$10,841.89	$10,841.89	$10,841.89	$10,841.89	$10,841.89	
Drug cost	$96,924	$144,224	$215,875	$251,213	$285,931	$994,166
Administration cost	$0	$0	$0	$0	$0	$0
Total cost per patient	$96,924	$144,224	$215,875	$251,213	$285,931	$994,166
Nusinersen costs						
Total doses	6	3	3	3	3	
Price per dose [b]	$110,000	$110,000	$110,000	$110,000	$110,000	
Drug cost	$660,000	$330,000	$330,000	$330,000	$330,000	$1,980,000
Administration cost	$2,616	$1,308	$1,308	$1,308	$1,308	$7,847
Total cost per patient	$662,616	$331,308	$331,308	$331,308	$331,308	$1,987,847
Incremental cost (risdiplam - nusinersen)						
Incremental drug cost	-$563,076	-$185,776	-$114,125	-$78,787	-$44,069	-$985,834
Incremental administration cost	-$2,616	-$1,308	-$1,308	-$1,308	-$1,308	-$7,847
Total incremental cost	-$565,692	-$187,084	-$115,433	-$80,095	-$45,377	-$993,681

[a] Risdiplam dosing based on the patient's age and body weight as per the Product Information. For a patient weighing 20 kg, the number of bottles per year would be 30.44.

[b] Published ex-manufacturer prices at the time of the submission, The nusinersen published ex-manufacturer price at the time of the evaluation was $104,500 (effective 1 May 2024).

Source: Tables 3.3, 3.5 and 3.6of the submission

6.41 The evaluation considered that the CMA should be based on both the dosing and cost of risdiplam and nusinersen based on their steady state doses (i.e. using risdiplam 5

mg/day and excluding nusinersen loading doses). The ESC agreed with the evaluation that the CMA should be based on both the dosing and cost of nusinersen based on their steady state doses (paragraph 6.33) and noted that the evaluation undertook a sensitivity analysis based on these parameters. The ESC further noted that as shown in Table 12, this resulted in identical annual drug cost for risdiplam and nusinersen with the only difference in cost due to the nusinersen administration costs.

Table 12: Results of cost-minimisation approach risdiplam versus nusinersen – steady state dosing (published drug prices) [a]

	Year 1	Year 2	Year 3	Year 4	Year 5	5 year total
Risdiplam costs						
Total bottles [b]	30.44	30.44	30.44	30.44	30.44	
Price per bottle [c]	$10,841.89	$10,841.89	$10,841.89	$10,841.89	$10,841.89	
Drug cost	$330,000	$330,000	$330,000	$330,000	$330,000	$1,650,000
Administration cost	$0	$0	$0	$0	$0	$0
Total cost per patient	$330,000	$330,000	$330,000	$330,000	$330,000	$1,650,000
Nusinersen costs						
Total doses	3	3	3	3	3	
Price per dose [c]	$110,000	$110,000	$110,000	$110,000	$110,000	
Drug cost	$330,000	$330,000	$330,000	$330,000	$330,000	$1,650,000
Administration cost	$1,308	$1,308	$1,308	$1,308	$1,308	$6,539
Total cost per patient	$331,308	$331,308	$331,308	$331,308	$331,308	$1,656,539
Incremental cost (risdiplam - nusinersen)						
Incremental drug cost	$0	$0	$0	$0	$0	$0
Incremental administration cost	-$1,308	-$1,308	-$1,308	-$1,308	-$1,308	-$6,539
Total incremental cost	-$1,308	-$1,308	-$1,308	-$1,308	-$1,308	-$6,539

[a] Steady state dosing: risdiplam = 5 mg/patient/day; nusinersen = 12 mg/dose, 3 doses/year (no loading doses)
[b] For steady state dosing patients weigh ≥20kg and the number of bottles per year is 30.44 based on a dose of 5 mg per day.
[c] Published ex-manufacturer prices at the time of the submission, The nusinersen published ex-manufacturer price at the time of the evaluation was $104,500 (effective 1 May 2024).
Source: Calculated during the evaluation based on the submission's spreadsheet Cost minimisation analyses.xlsx

6.42 The CMA presented in the submission was calculated using the published AEMP for risdiplam and nusinersen, as the nusinersen effective price was not available to the sponsor at the time of submission.

6.43 No risdiplam wastage was accounted for in the CMA, likely resulting in an underestimate of the amount of risdiplam dispensed. For the March 2023 risdiplam submission, DUSC considered scripts per year to be underestimated particularly in older children due to wastage associated with liquid formulations (paragraphs 6.78 and 6.86, risdiplam PSD, March 2023 PBAC meeting).

6.44 The submission did not present a CMA to compare risdiplam versus ONA.

Drug cost/patient/year $330,000 (published price, steady state dose)

6.45 In the CMA presented in the submission, the risdiplam drug cost/patient/year was estimated to be $96,924 in Year 1, increasing to $285,931 in Year 6, assuming no discontinuations or wastage. This was based on the published price of risdiplam with dosing based on the patient's weight and age.

6.46 Based on a steady state dose (5 mg per day), risdiplam was estimated to cost $330,000 per patient per year, assuming no discontinuations or wastage, based on the published price of risdiplam.

6.47 The number of bottles of risdiplam used per patient as presented in the CMA in the submission, in the CMA using risdiplam steady state dosing (5 mg/day) and as presented in the financial estimates are presented in Table 13.

6.48 The difference in the number of bottles in the CMA and the financial estimates in year 1 was due to different methods of estimating patient weight. The CMA estimated the weight every month whereas the financial estimates used an average weight based on the weight at the end of a treatment period. The difference in subsequent years was due to the average for the number of bottles in the financial estimates including incident patients (who use fewer bottles) as well as prevalent patients. These figures also demonstrate the difference in the number of bottles used per patient depending on whether calculations use risdiplam weight-based dosing or steady state dosing.

Table 13: Number of bottles of risdiplam used per patient per year

	Risdiplam, number of bottles used per patient					
	Year 1	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**5 year total**
CMA as presented in the submission [a]	8.94	13.30	19.91	23.17	26.37	91.70
CMA using steady state dosing	30.44	30.44	30.44	30.44	30.44	152.2
Financial estimates [a, b]	10.75	14.37	16.71	18.67	20.46	80.95

CMA = cost-minimisation approach

a Calculated using risdiplam weight-based dosing.

b Calculated based on the total number of bottles dispensed per year / total number of patients on therapy.

Source: Calculated during the evaluation based on the submission's spreadsheets Cost minimisation analyses.xlsx and Section 4 Workbook.xlsx

Estimated PBS usage & financial implications

6.49 This submission was not considered by DUSC.

6.50 The submission used an epidemiological approach to estimate the financial impact of listing risdiplam for the pre-symptomatic treatment of SMA patients with three *SMN2* copies on the PBS using published drug prices.

6.51 The key data sources, parameters and assumptions used to estimate the financial impact are summarised in Table 14.

Table 14: Data sources and parameter values applied in the utilisation and financial estimates

Data	Value and source	Comment
Eligible population		
Screening for SMA	All newborn babies in Australia were assumed to be screened for SMA at birth.	Reasonable as NBS for the detection of SMA has been rolled out nationally.
Live births	**Year** / **Live births**: 2025: 362,706; 2026: 366,687; 2027: 370,252; 2028: 373,433; 2029: 376,318; 2030: 379,018. Source: ABS projection, series B birth data, 2025-2030	Values could not be verified. 3222.0 Population projection series B released 29/11/23 estimated 349,038 Australians will be aged 0 in 2025 increasing to 359,104 in 2030, which were lower than the submission's values.
Incidence of SMA with 3 *SMN2* gene copies	Australian data (D'Silva 2021) reported an incidence of 21/252,081 genetically identified patients with SMA (equivalent to 1 in 12,004 or 8.33 per 100,000). Of the patients diagnosed with SMA, 38.1% had 3 *SMN2* copies.	These estimates were lower than those accepted by the PBAC at the July 2023 consideration of nusinersen (8.66 per 100,000 live births, 45.81% with 3 copies of *SMN2*) (Table 20, nusinersen PSD, July 2023 PBAC meeting). These figures were explored in sensitivity analyses conducted during the evaluation.
Treatment utilisation		
Age of treatment initiation	One month, as it closely aligned with the age at first dose for patients with 3 *SMN2* gene copies observed in the RAINBOWFISH study, i.e. mean = 29.9 days, median = 28.0 days (range 20-41 days). Source: RAINBOWFISH Primary CSR	In the CMA the mean age of treatment initiation from RAINBOWFISH was used as a guide to approximate the age at which risdiplam is initiated. Given the introduction of NBS in Australia, the one month age of treatment initiation was reasonable for the majority of patients (newborns), but not for any prevalent or grandfathered patients or patients switching from nusinersen to risdiplam.
Risdiplam uptake rate	Based on expert opinion, the submission assumed that 60% of patients with SMA with 3 copies of *SMN2* would receive ONA and 40% of patients would not receive ONA due to patients not meeting the threshold for AAV9 or personal choice. For the patients not receiving ONA, it was assumed that half (20%) receive risdiplam and half (20%) receive nusinersen.	It was reasonable that ONA would be used by most SMA patients who are eligible to receive it for convenience reasons, however some families could opt for risdiplam treatment due to its oral administration or ready availability. The evaluation and the ESC considered that it therefore may not be reasonable to assume that risdiplam will be used only in patients for whom ONA was not suitable, and risdiplam may substitute for ONA in some patients. Further, it may not be reasonable to assume that nusinersen and risdiplam would have the same market share, as most Advisors to the sponsor (comprised of 5 experienced paediatric neuromuscular experts in SMA) reported that they expect to treat more pre-symptomatic patients with risdiplam than nusinersen.

Data	Value and source		Comment
Risdiplam dose	Dosing was based on the risdiplam dosing regimen with treatment assumed to commence when the patient is one month of age. The dose required for patients in each year whilst they are on treatment was estimated based on the patient's expected weight at the end of the continuation period. (Patient weight estimated using WHO Child Growth Standards, 50th percentile). Based on their body weight, patients were dispensed 1, 2 or 3 bottles of risdiplam per script.		Reasonable, although the calculations slightly overestimate the number of risdiplam bottles required per year due to the assumption that the patient's weight is as expected at the end of the continuum period, rather than increasing gradually over each time period.
DMT discontinuation	It was assumed that no patients discontinued risdiplam treatment due to AEs or any other reasons.		It may be reasonable to assume that patients continue DMT over the first 6 years of their life, however there is no data to support this assumption over a longer duration.
DMT switching	The submission assumed that no patients switched to receive risdiplam after receiving another DMT and that no patients switched to another DMT after receiving risdiplam.		This may not be reasonable. Patients are able to receive risdiplam and then switch to nusinersen or first receive nusinersen and then switch to risdiplam.
Mortality	Survival for patients treated pre-symptomatically with risdiplam or nusinersen with 3 *SMN2* gene copies was assumed to be 100% whilst on treatment as no patients have died whilst on treatment in the RAINBOWFISH and NURTURE studies during follow-up of 20 months for risdiplam and 60 months for nusinersen.		This was consistent with the data available for the requested patient population.
Prevalent patients	No prevalent patients were assumed at the start of the utilisation. The submission (p85) claimed this was due to the speed of symptom onset for SMA and the availability of DMT.		This may not be reasonable. NBS was recently rolled out across Australia and patients with SMA with 3 copies of *SMN2* born before the implementation of NBS may not yet have received treatment. These patients could potentially initiate risdiplam before the age of 36 months in line with the proposed restriction. Consequently, the submission may have underestimated the number of patients who will receive risdiplam under the proposed listing.
Grandfathered patients	The submission assumed there would be no grandfathered patients.		The submission noted that 8 pre-symptomatic Australian SMA patients (including 6 patients with 3 copies of *SMN2*) are currently accessing risdiplam via the RAINBOWFISH study and may be eligible for PBS supply. Consequently, the submission may have underestimated the number of patients who will receive risdiplam under the proposed listing. These patients would commence PBS-reimbursed treatment at a higher dose than newborns.
Costs			
Proposed risdiplam	$10,841.89	Published price (AEMP)	
Nusinersen	$110,000	Published price (AEMP)	

<table>
<tr><th>Data</th><th>Value and source</th><th>Comment</th></tr>
<tr><td>MBS costs (nusinersen administration)</td><td>
<table>
<tr><th>MBS item and description</th><th>MBS item</th><th>MBS cost</th></tr>
<tr><td>Professional attendance by specialist</td><td>105</td><td>$48.05</td></tr>
<tr><td>Anaesthetist, pre-anaesthesia consultation</td><td>17610</td><td>$48.05</td></tr>
<tr><td>Initiation of management of anaesthesia for lumbar puncture</td><td>21945</td><td>$109.00</td></tr>
<tr><td>Anaesthesia, perfusion or assistance at anaesthesia</td><td>23010</td><td>$21.80</td></tr>
<tr><td>Intrathecal initial injection including <1 hour of attendance by the medical practitioner</td><td>18216</td><td>$209.05</td></tr>
</table>
Source: Table 4.20, p98 of the submission
Costs shown reflect 100% MBS benefits.
80% MBS benefit applied in the financial estimates.</td><td>Reasonable and consistent with current MBS costs and the resource costs used in the CMA.
These were also consistent with the nusinersen submission evaluated at the July 2023 PBAC meeting (paragraph 6.63, nusinersen PSD, July 2023).</td></tr>
<tr><td>Adverse events</td><td>Any costs and resource utilisation associated with AEs were not included in the financial estimates.</td><td>This was consistent with the CMA presented.</td></tr>
</table>

AAV9 = high adeno-associated viral vector serotype 9; ABS = Australian Bureau of Statistics; AE = adverse event; AEMP = Australian ex-manufacturer price; CMA = cost=minimisation approach; CSR = clinical study report; DMT = disease modifying therapy; NBS = newborn bloodspot screening; ONA = onasemnogene abeparvovec; SMA = spinal muscular atrophy; SMN = survival of motor neuron

a - In sheet '2e. Scripts – market' presented in the submission, cell G351 shows that 11 patients received risdiplam PBS item 12606L during 2023 under the concessional safety net but these services were not included in the calculations for determining the average weighted copayment for risdiplam and the ratio of public to private use for risdiplam. However, the inclusion of these 11 patients in these calculations made a negligible difference to the overall financial estimates and therefore this was not corrected during the evaluation.

Source: Tables 4.2 and 4.3 of the submission; Section 4 Workbook.xlsx

6.52 Table 15 presents the estimated net financial implications for the proposed listing of risdiplam as shown in the submission, which used published drug. At year 6, the estimated number of patients was 32 and the net saving to the PBS would be $2,075,149. The estimated financial implications for the PBS were cost saving due to the use of weight-based dosing for risdiplam (which minimised risdiplam drug costs in years 1 to 6 of treatment) and the inclusion of loading doses for nusinersen (which increased the cost of the nusinersen affected scripts in year 1 of treatment).

Table 15: Estimated financial impact of the requested risdiplam PBS listing for the PBS/RPBS and for the health budget (published drug prices)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimation of use and financial impact of the proposed medicine (PBS)						
Incident patients with SMA	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1
Proportion with 3 *SMN2* copies (38.1%)	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1
Patients seeking pre-symptomatic SMA treatment (100%)	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1
Patients initiating treatment with risdiplam (20% uptake)	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1
Patients continuing treatment with risdiplam (100%)	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1
Total patients on risdiplam [a]	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1
Number of risdiplam scripts						
Initiating scripts	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1
Continuing scripts	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1
Total	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1
Number of risdiplam 60 mg bottles dispensed [b]	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1
PBS cost for risdiplam (pub)						
PBS drug cost for risdiplam (pub)	[redacted]2	[redacted]2	[redacted]2	[redacted]2	[redacted]2	[redacted]2
PBS patient co-payment	[redacted]3	[redacted]3	[redacted]3	[redacted]3	[redacted]3	[redacted]3
Total (pub)	[redacted]2	[redacted]2	[redacted]2	[redacted]2	[redacted]2	[redacted]2
Estimation of changes in use and financial impact of other medicines (PBS)						
Patients not receiving nusinersen [b]	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1
Change in nusinersen scripts [c]	-[redacted]1	-[redacted]1	-[redacted]1	-[redacted]1	-[redacted]1	-[redacted]1
PBS cost of nusinersen (pub)						
PBS drug cost for nusinersen (pub)	[redacted]3	[redacted]3	[redacted]3	[redacted]3	[redacted]3	[redacted]3
PBS patient co-payment	[redacted]2	[redacted]2	[redacted]2	[redacted]2	[redacted]2	[redacted]2
Total (pub)	[redacted]3	[redacted]3	[redacted]3	[redacted]3	[redacted]3	[redacted]3
Estimated financial implications for the PBS						
Net cost to PBS (pub)	[redacted]3	[redacted]3	[redacted]3	[redacted]3	[redacted]3	[redacted]3
Estimated financial implications for the health budget						
Net MBS costs	[redacted]3	[redacted]3	[redacted]3	[redacted]3	[redacted]3	[redacted]3
Net cost to Govt health budget (pub)	[redacted]3	[redacted]3	[redacted]3	[redacted]3	[redacted]3	[redacted]3

govt = government; MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; pub = published; RIS = risdiplam; SMA = spinal muscular atrophy; SMN = survival of motor neuron

a Totals may not add up due to rounding.

b Depending on age and body weight, patients can be dispensed either 1, 2 or 3 bottles of risdiplam (60 mg) per script.

c The number of patients who would no longer receive nusinersen was assumed to be equal the number of patients who would initiate risdiplam.

d The number of doses of nusinersen that would no longer be received was assumed to include 6 doses in year 1 (including loading doses) and 3 doses in subsequent years (steady state dose).

Source: Tables 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 4.10, 4.12, 4.13, 4.14, 4.15, 4.16, 4.17, 4.18, 4.19, 4.20, 4.21 and 4.22of the submission.

The redacted values correspond to the following ranges
1 < 500
2 $0 to < $10 million
3 net cost saving

6.53 While the submission estimated the total impact to government to be cost saving for each year over the first six years of listing, these figures were based on published prices for risdiplam and nusinersen. Additionally, as risdiplam is to be given as a life-

long therapy and patients were assumed to not discontinue treatment, the total use of risdiplam will continue to rise beyond six years.

6.54 The submission did not include any grandfathered patients in the financial estimates. Eight pre-symptomatic Australian SMA patients, including six patients with three copies of *SMN2*, were accessing risdiplam as part of the RAINBOWFISH study at the time of the submission. These six patients would not have been accounted for in the incident population. The impact of these patients on the financial estimates was unclear as it was unknown what treatment these patients would receive once they complete RAINBOWFISH in the absence of PBS listing for risdiplam in pre-symptomatic SMA in patients with three copies of *SMN2*. If these patients would not have initiated nusinersen, then the financial estimates may be underestimated as they would represent additional market growth for risdiplam only. However, if these patients would have switched to nusinersen following their participation in RAINBOWFISH, the impact on the financial estimates would be negligible.

6.55 The submission stated that treatment uptake rates were informed based on internal assumptions following consultation with advisors (pre-symptomatic SMA prescribers). The submission claimed that the majority of families will elect for one-time treatment with ONA (~60%) and the remaining 40% of patients will be divided evenly between risdiplam and nusinersen; however, these figures were based on assumptions. While it may be reasonable to assume that ONA is used most commonly, some families could opt to initiate risdiplam, favouring it over ONA because of its oral administration or ready availability. Further, it may not be reasonable to assume that nusinersen and risdiplam would have the same market share, as the submission reported that advisors to the sponsor expect to treat more pre-symptomatic patients with risdiplam than nusinersen. Consequently, the evaluation and the ESC considered the assumption that 20% of eligible patients would receive risdiplam is likely to be underestimated.

6.56 The submission assumed that the uptake of risdiplam did not include any treatment switching either to or from other DMTs. The evaluation and the ESC considered this may not be reasonable as patients can use risdiplam after nusinersen (and vice versa). Whether there would be cost savings associated with risdiplam depends on the degree of substitution for nusinersen and ONA. When considering the proposed listing for ONA for patients aged less than 9 months with pre-symptomatic SMA with 1-3 copies of the *SMN2* gene, the PBAC considered that seven years was a reasonable duration for the basis of the cost-minimisation analysis (comparator nusinersen) (paragraph 8.11, ONA PSD, May 2021 PBAC meeting). As such, compared to ONA, treatment with risdiplam will be less expensive in the shorter term, but beyond seven years, treatment with ONA will be less expensive than risdiplam.

6.57 Overall, the evaluation and the ESC considered the utilisation of risdiplam was likely underestimated as:

- The incidence of SMA (8.33 per 100,000) and proportion with three *SMN2* copies (38.1%) assumed in the submission were lower than what was previously accepted

by the PBAC for nusinersen at the July 2023 meeting (8.66 per 100,000 and 45.81%, respectively; Table 20, nusinersen PSD, July 2023);

- The uptake rate for risdiplam may be underestimated. Advisors to the Sponsor suggested that they expect to treat more pre-symptomatic patients with risdiplam than nusinersen; and
- No substitution for ONA was considered by the resubmission. As the resubmission noted, caregivers of patients may have reservations around ONA as a gene therapy, though it may still be preferred if the alternative was a thrice yearly intrathecal injection. Risdiplam, as an oral therapy, would represent an alternative which may be more tolerable for caregivers and may in fact be preferred by caregivers who have reservations around ONA.

However as discussed in paragraph 6.59, the impact of the underestimate depends on whether nusinersen or ONA was substituted for. If risdiplam substituted for nusinersen, then underestimating risdiplam utilisation likely would have a slight cost saving or no impact (assuming cost neutrality). However, if risdiplam substituted for ONA, then the financial impacts may be underestimated in the long run (although not within the six years of the forward estimates) as risdiplam needs to be administered lifelong whereas ONA is intended to be a once-off injection.

For more detail on PBAC's view, see section 7 PBAC outcome.

Financial Management – Risk Sharing Arrangements

6.58 No subsidisation cap was proposed in the submission. The submission stated that the sponsor is willing in principle to enter into the existing risk sharing arrangement in place for pre-symptomatic SMA patients with three *SMN2* gene copies.

7 PBAC Outcome

7.1 The PBAC recommended the listing of risdiplam for the pre-symptomatic initiation of treatment in patients aged <36 months, genetically diagnosed with spinal muscular atrophy (SMA), who have a survival motor neuron 2 (*SMN2*) gene copy number of 3, on the basis that it should be available only under special arrangements under Section 100. The PBAC's recommendation for listing was based on, among other matters, its assessment, as described above, that the cost-effectiveness of risdiplam would be acceptable if it were cost minimised against nusinersen.

7.2 The PBAC's recommendation was based on equi-effective doses of 5 mg of risdiplam daily and nusinersen 12 mg (5 mL) per administration every 4 months (3 per year, i.e. excluding nusinersen loading doses) consistent with its previous advice for the pre-symptomatic initiation of risdiplam in patients with SMA and an *SMN2* gene copy number of 1 or 2 (paragraph 7.2, risdiplam PSD, March 2023 PBAC meeting).

7.3 The PBAC acknowledged there is a clinical need for an orally administered treatment, noting consumer comments that there were current inequities with lack of access for

patients with 3 copies of the *SMN2* gene.

7.4 The PBAC considered it was reasonable for the risdiplam initial and continuing restrictions for pre-symptomatic SMA in patients with 3 copies of *SMN2* to be separate from restrictions for patients with 1-2 copies of *SMN2.*

7.5 The PBAC considered it was reasonable to remove the treatment criteria proposed in the submission for patients to be either untreated or treated with non-PBS subsidised supply. The PBAC considered that removing this would: i) allow patients initiated pre-symptomatically on nusinersen to be switched to risdiplam and, ii) still ensure that grandfathered patients would be eligible to access risdiplam. The PBAC noted this change to the proposed restriction would be consistent with the risdiplam initial listing for patients with pre-symptomatic SMA with 1-2 copies of the *SMN2* gene.

7.6 The PBAC considered the submission appropriately nominated nusinersen as the main comparator given it is expected that nusinersen would be the main treatment replaced.

7.7 The PBAC noted the clinical evidence presented was primarily based on unanchored numerical comparisons of point estimates for several outcomes using single arm studies to compare risdiplam (RAINBOWFISH) and nusinersen (NURTURE). The PBAC noted that patient numbers were low, with RAINBOWFISH enrolling 13 patients (13/26 patients = 50%) and NURTURE enrolling 10 patients (10/25 patients = 40%) who had three copies of *SMN2*. The PBAC considered that the studies had a high risk of bias.

7.8 The PBAC noted that comparisons between RAINBOWFISH and NURTURE were made only on point estimates of change from baseline in HINE-2 scores and CHOP-INTEND scores as statistical comparisons were likely unreliable. The PBAC noted that no minimal clinically important difference was proposed to allow assessment of non-inferiority. The PBAC noted that patients in RAINBOWFISH had higher motor functioning status at baseline, and considered this may have biased the results of the unanchored comparison in favour of risdiplam. Overall, the PBAC considered that the evidence provided was of poor quality. However, the PBAC considered that the clinical claim of non-inferior efficacy, while poorly supported, was clinically plausible, consistent with previous comparisons between risdiplam and nusinersen, noting the limitations of the data available.

7.9 The PBAC considered that the claim of non-inferior comparative safety, with a favourable safety profile in some patients, was reasonable. The PBAC recalled it had previously acknowledged that a conclusion of a favourable safety profile for risdiplam over nusinersen in some patients was reasonable given the less invasive route of administration (para 7.8, risdiplam PSD, March 2021 PBAC meeting; para 7.7, risdiplam PSD, March 2023 meeting).

7.10 The submission presented a cost-minimisation approach. The PBAC noted that the proposed equi-effective doses included weight-based dosing of risdiplam for

paediatric patients who commence treatment at the age of one month, rather than maintenance (steady state) dosing. The PBAC noted this increased the cost-minimised price for risdiplam and considered this was not justified as treatment is likely to be life-long and doses are higher in older infants and children.

7.11 The PBAC noted that the submission proposed equi-effective doses that incorporated loading doses for nusinersen, rather than maintenance (steady state) dosing. The PBAC noted this increased the cost-minimised price for risdiplam and considered it was not justified. The PBAC noted that the cost-minimisation approach excluded the cost of administration of nusinersen, consistent with its previous recommendation (para 7.9, risdiplam PSD, March 2023 PBAC meeting), and the Committee considered this was appropriate.

7.12 The PBAC noted that where cost per patient calculations are uncertain, the guiding principle is that the Australian Government should not bear the financial risk of this uncertainty because the Australian population already has access to therapy that is at least as effective and safe. As in its previous advice, the PBAC considered that a conservative approach (assuming that all patients treated with risdiplam would require 5 mg per day and excluding costs for nusinersen loading doses and administration) was appropriate, given the limitations of the available evidence for risdiplam and nusinersen and the high treatment costs. The PBAC also recalled DUSC's comments regarding the potential for additional wastage with risdiplam due to its liquid formulation for administration, which was not accounted for in the proposed equi-effective dose calculations.

7.13 The PBAC noted that ONA was a potential alternative therapy, although given the differences in mechanism of action and administration (once off versus continuous) expected risdiplam and ONA to primarily be used in different patient populations. The PBAC noted that risdiplam would be less expensive than ONA in the initial years of treatment, and a comparison of costs over the longer-term would be uncertain due to the lack of long-term clinical data.

7.14 The submission took an epidemiological approach to estimate the number of eligible patients likely to receive treatment with risdiplam under the proposed restriction and the PBAC considered that this was appropriate because there was insufficient data for nusinersen in the proposed population to inform a market share approach (<3 months). The PBAC considered most of the submission's assumptions to be reasonable, with the following exceptions: the submission i) had likely underestimated the incidence of SMA, ii) did not estimate the impact of treatment switching, and iii) did not factor in the likelihood that some patients would be grandfathered onto PBS treatment. In addition, the Committee considered that the market share for risdiplam is likely to be greater than for nusinersen given the oral route of administration. Overall, the PBAC considered the submission had underestimated the use of risdiplam. However, as the estimates assume a small initial cost-saving associated with risdiplam

(due to lower doses in newborns), following which the listing would be cost-neutral, this underestimate would not result in additional costs to the PBS/RPBS.

7.15 The PBAC considered that flow-on changes to the ONA restrictions would be required to allow patients with 3 copies of the *SMN2* gene to switch from pre-symptomatic treatment with risdiplam to ONA.

7.16 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because risdiplam is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over nusinersen, or not expected to address a high and urgent unmet clinical need given the presence of an alternative therapy, the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were not met.

7.17 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:
Recommended

8 Recommended listing

8.1 Amend existing/recommended listing as follows:

MEDICINAL PRODUCT **medicinal product pack**	**PBS item code**	**Max. qty packs**	**Max. qty units**	**№.of Rpts**	**Available brands**
RISDIPLAM					
risdiplam 750 microgram/mL powder for oral liquid, 80 mL	NEW (private)	1	1	0	Evrysdi
risdiplam 750 microgram/mL powder for oral liquid, 80 mL	NEW (public)	1	1	0	Evrysdi

Restriction Summary [new]		
Concept ID (for internal Dept. use)		**Category / Program:** Section 100 – Highly Specialised Drugs Program
		Prescriber type: ☒Medical Practitioners
		Restriction type: ☒Authority Required (FULL assessment) in writing only via post/HPOS upload)
		Authority type: ☒ Complex Authority Required (CAR)
Prescribing rule level		**Administrative Advice:** No increase in the maximum number of repeats may be authorised.
Prescribing rule level		**Administrative Advice:** Special Pricing Arrangements apply.
		Administrative Advice: Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday)., Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au, Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos, Or mailed to:, Services Australia, Complex Drugs, Reply Paid 9826, HOBART TAS 7001
		Prescribing Instructions: The quantity of drug and number of repeat prescriptions prescribed is to be in accordance with the relevant 'Note' attached to this listing.
		The approved Product Information recommended dosing is as follows: (i) 16 days to less than 2 months of age: 0.15 mg/kg (ii) 2 months to less than 2 years of age: 0.20 mg/kg (iii) 2 years of age and older weighing less than 20 kg: 0.25 mg/kg (iv) 2 years of age and older weighing 20 kg or more: 5 mg
		Prescribing Instructions: In this authority application, state which of (i) to (iv) above applies to the patient. Based on (i) to (iv), prescribe up to: 1 unit where (i) applies; 2 units where (ii) applies; 3 units where (iii) applies; 3 units where (iv) applies.
		Indication: Pre-symptomatic Spinal Muscular Atrophy (SMA)
		Treatment Phase: Initial treatment of pre-symptomatic spinal muscular atrophy (SMA) with 3 copies of the *SMN2* gene
		Treatment criteria:

	Must be treated by a specialist medical practitioner experienced in the diagnosis and management of SMA associated with a neuromuscular clinic of a recognised hospital in the management of SMA; or in consultation with a specialist medical practitioner experienced in the diagnosis and management of SMA associated with a neuromuscular clinic.
	Clinical criteria:
	The condition must have genetic confirmation of 5q homozygous deletion of the survival motor neuron 1 (*SMN1*) gene; or
	The condition must have genetic confirmation of deletion of one copy of the *SMN1* gene in addition to a pathogenic/likely pathogenic variant in the remaining single copy of the *SMN1* gene
	AND
	Clinical criteria:
	The condition must be pre-symptomatic SMA, with genetic confirmation that there are 3 copies of the survival motor neuron 2 (SMN2) gene
	AND
	Clinical criteria:
	The treatment must be given concomitantly with best supportive care for this condition
	AND
	Clinical criteria:
	Patient must be untreated with gene therapy
	Population criteria:
	Patient must be aged under 36 months prior to commencing treatment
	Prescribing Instructions: Application for authorisation of initial treatment must be in writing (lodged via postal service or electronic upload) and must include: (a) details of the proposed prescription; and, (b) a completed Spinal muscular atrophy PBS Authority Application Form which includes the following: (i) confirmation of genetic diagnosis of SMA; and (ii) a copy of the results substantiating the number of *SMN2* gene copies determined by quantitative polymerase chain reaction (qPCR) or multiple ligation dependent probe amplification (MLPA)
	Administrative Advice: An outcome on the authority application is not immediate, but will follow in due course. Electronic upload is encouraged to reduce processing time.

MEDICINAL PRODUCT **medicinal product pack**	**PBS item code**	**Max. qty packs**	**Max. qty units**	**№.of Rpts**	**Available brands**
RISDIPLAM					
risdiplam 750 microgram/mL powder for oral liquid, 80 mL	NEW (private)	1	1	5	Evrysdi
risdiplam 750 microgram/mL powder for oral liquid, 80 mL	NEW (public)	1	1	5	Evrysdi
Restriction Summary [new]					
Concept ID (for internal Dept. use)	**Category / Program:** Section 100 – Highly Specialised Drugs Program				
	Prescriber type: ☒Medical Practitioners				
	Restriction type: ☒Authority Required (immediate assessment) the prescriber can apply via telephone/online channels and get an immediate outcome at the end of the interaction				

		Authority type: ☒ Complex Authority Required (CAR)
Prescribing rule level		**Administrative Advice:** No increase in the maximum number of repeats may be authorised.
Prescribing rule level		**Administrative Advice:** Special Pricing Arrangements apply.
		Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).
		Prescribing Instructions: The quantity of drug and number of repeat prescriptions prescribed is to be in accordance with the relevant 'Note' attached to this listing. The approved Product Information recommended dosing is as follows: (i) 16 days to less than 2 months of age: 0.15 mg/kg (ii) 2 months to less than 2 years of age: 0.20 mg/kg (iii) 2 years of age and older weighing less than 20 kg: 0.25 mg/kg (iv) 2 years of age and older weighing 20 kg or more: 5 mg
		Prescribing Instructions: In this authority application, state which of (i) to (iv) above applies to the patient. Based on (i) to (iv), prescribe up to: 1 unit where (i) applies; 2 units where (ii) applies; 3 units where (iii) applies; 3 units where (iv) applies.
		Indication: Pre-symptomatic Spinal Muscular Atrophy (SMA)
		Treatment Phase: Continuing/maintenance treatment of pre-symptomatic spinal muscular atrophy (SMA) with 3 copies of the *SMN2* gene
		Treatment criteria:
		Must be treated by a specialist medical practitioner experienced in the diagnosis and management of SMA associated with a neuromuscular clinic of a recognised hospital in the management of SMA; or in consultation with a specialist medical practitioner experienced in the diagnosis and management of SMA associated with a neuromuscular clinic.
		AND
		Treatment criteria:
		Patient must not be undergoing treatment through this 'Continuing treatment' listing where the most recent PBS authority approval for this PBS-indication has been for gene therapy.
		Clinical criteria:
		Patient must have previously received PBS-subsidised treatment with this drug for this condition; OR
		Patient must be eligible for continuing PBS-subsidised treatment with nusinersen for this condition
		AND
		Clinical Criteria
		The treatment must not be in combination with PBS-subsidised treatment with nusinersen for this condition
		AND
		Clinical criteria:
		The treatment must be given concomitantly with best supportive care for this condition

	AND
	Clinical criteria:
	The treatment must be ceased when invasive permanent assisted ventilation is required in the absence of a potentially reversible cause while being treated with this drug
	Population Criteria:
	Patient must have been 18 years of age or younger at the time of initial treatment with this drug
	Prescriber instructions
	Invasive permanent assisted ventilation means ventilation via tracheostomy tube for greater than or equal to 16 hours per day.
	In a patient who wishes to switch from PBS-subsidised nusinersen to PBS-subsidised risdiplam for this condition a wash out period may be required.

Flow on to "switch" listing for Zolgensma® (onasemnogene abeparvovec)

Amend the Treatment Phase (as per 1 August listing) to include risdiplam (currently only allows switch from nusinersen to zolgensma).

Treatment phase: Use occurring after treatment with at least one disease modifying therapy for this condition (i.e. switching from nusinersen/risdiplam to onasemnogene abeparvovec)

- ***The restriction sits under the PBS item codes for 3 copies of SMN2 gene as below:***
  13674Q 13663D 13671M 13678X 13669K 13670L 13665F 13682D 13672N 13667H 13683E 13680B 13664E 13681C 13677W 13675R 13679Y 13662C 13673P 13668J 13666G 13676T

***This restriction may be subject to further review. Should there be any changes made to the restriction the sponsor will be informed*.**

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

10 Sponsor's Comment

The sponsor had no comment.