

**7.08 RISDIPLAM,  
Powder for oral solution 0.75 mg per 1 mL,  
80 mL,  
Evrysdi<sup>®</sup>,  
Roche Products Pty Ltd.**

**1 Purpose of submission**

1.1 The standard re-entry resubmission requested a Section 100, Authority Required (written) listing for risdiplam for the treatment of:

- (i) **Population 1** - adults diagnosed with 5q spinal muscular atrophy (SMA) with symptom onset prior to 19 years of age and no initiation of disease-modifying treatment (DMT) during childhood;
- (ii) **Population 2** - patients aged <36 months with a confirmed genetic diagnosis of SMA (SMA1 deletion or mutation) who have an *SMN2* gene copy number of 1 or 2 and are pre-symptomatic; and
- (iii) **Population 3** - patients aged <36 months with a confirmed genetic diagnosis of SMA (*SMA1* deletion or mutation) who have a *SMN2* gene copy number of 3 and are pre-symptomatic.

1.2 Listing was requested on the basis of:

- Population 1 – a cost-minimisation analysis versus nusinersen;
- Population 2 – a cost-minimisation analysis versus nusinersen; and
- Population 3 - a cost-minimisation analysis versus onasemnogene abeparvovec (ONA).

**Table 1: Key components of the clinical issue addressed by the resubmission**

Component	Description		
	Population 1	Population 2	Population 3
Population	Adults (≥19 years-old) diagnosed with SMA <sup>a</sup> with symptom onset ≤18 years of age	Infants (<36 months-old) diagnosed with SMA <sup>a</sup> who are pre-symptomatic and have an SMN2 gene copy number of 1 or 2	Infants (<36 months-old) diagnosed with SMA <sup>a</sup> who are pre-symptomatic and have an SMN2 gene copy number of 3
Intervention	Risdiplam orally administered for solution as chronic treatment taken daily <sup>b</sup>		
Comparator	Nusinersen intrathecally administered solution for injection as chronic treatment		Onasemnogene abeparvovec gene therapy as a one-time treatment
Outcomes	-Mean difference versus baseline HFMSE -Mean difference versus baseline RULM -Mean difference versus baseline MFM32	-Event free survival -Overall survival -CHOP-INTEND total score -Individual motor milestone achievements as measured by the HINE-2 -Sitting without support after 12 months of treatment	-Event free survival -Overall survival -Individual motor milestone achievements as measured by HINE-2 and WHO criteria <sup>c</sup>
Clinical claim	In adult SMA patients with symptom onset prior to 19 years of age (primarily SMA Types 2 and 3), risdiplam is non-inferior in terms of efficacy and safety compared with nusinersen, with a favourable safety profile in some patients due to differences in administration (oral vs intrathecal).	In pre-symptomatic SMA patients with genetically confirmed SMN1 deletion or mutation and a SMN2 gene copy number of 1 or 2, risdiplam is non-inferior in terms of efficacy and safety compared with nusinersen, with a favourable safety profile in some patients due to differences in administration (oral vs intrathecal).	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 onasemnogene abeparvovec, with a favourable safety profile in some patients due to differences in therapy type (oral vs gene therapy).

Source: Table 1.1 p3-4 of the resubmission

CHOP-INTEND=Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HFMSE=Hammersmith functional motor scale expanded; HINE-2=Hammersmith Infant Neuromuscular Examination; MFM32=motor function measure 32; RULM=revised upper limb module; SMA = spinal muscular dystrophy; SMN = survival motor neuron

a – Defined as genetic confirmation of 5q homozygous deletion of the survival motor neuron 1 (SMN1) gene OR genetic confirmation of deletion of one copy of the SMN1 gene in addition to a pathogenic / likely pathogenic variant in the remaining single copy of the SMN1 gene.

b – Dosage dependent on age and weight, with maximum daily dose of 5mg.

c - Motor milestones were measured by the Hammersmith Infant Neurological Examination – Module 2(HINE-2) in the RAINBOWFISH trial and by world health organisation (WHO) criteria in the SPR1NT trial. The comparison assumed equivalence between the WHO motor milestones and HINE-2 motor milestones

1.3 The Pre-Sub-Committee Response (PSCR) acknowledged that ONA was not recommended in population 3 at the November 2022 meeting and stated that the sponsor does not intend to conduct a cost-effectiveness analysis compared to best supportive care for resubmission. The ESC considered that on this basis, population 3 was effectively withdrawn from the submission. The PSCR suggested that if ONA or nusinersen is recommended in population 3 in the future, the PBAC could recommend that changes to the listings also flow on to risdiplam.

## 2 Background

### Registration status

- 2.1 Risdiplam was approved for registration by the TGA on the 2 June 2021 ‘for the treatment of 5q spinal muscular atrophy (SMA) in patients aged 2 months and older’. At the time of PBAC consideration the Delegate’s Overview was available for the submission to extend the TGA indication for risdiplam to include patients under the age of two months.

### Previous PBAC consideration

- 2.2 At the March 2021 PBAC meeting risdiplam was recommended for listing for treatment of SMA Type 1, 2 or 3a in patients aged 18 years or less, based on non-inferiority to nusinersen.
- 2.3 At the March 2021 PBAC meeting risdiplam was not recommended for listing for Type 1, 2 or 3 SMA patients aged >18 years old. At that time, the PBAC considered the claim of superior efficacy of risdiplam over best supportive care (BSC) in this population was not supported by the clinical evidence and therefore the cost-utility analysis was not informative (para 7.23, risdiplam public summary document (PSD), March 2021 PBAC meeting). Nusinersen has since been listed on the PBS for patients aged ≥19 years old with ≥1 symptoms present before the age of 19 after receiving a positive recommendation at the March 2022 PBAC meeting, meaning the relevant comparator for population 1 is now nusinersen.
- 2.4 The PBAC has not previously considered risdiplam for treatment of pre-symptomatic SMA patients.
- 2.5 The resubmission did not address the type 3b SMA population. Nusinersen was recommended in the Type 3b population at the July 2021 PBAC meeting, and the PBAC advised that this extension to include paediatric patients with symptom-onset between age 3 and 18 years [i.e., Type 3b] could also be flowed onto risdiplam using the equi-effective doses established for Type 1, 2 and 3a [from the risdiplam versus nusinersen cost-minimisation used to inform the risdiplam recommended listing] (para 7.23, nusinersen PSD, July 2021 PBAC meeting). At the time of PBAC consideration the sponsor had not progressed this proposed extension to the risdiplam listing to include Type 3b patients.

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

## 3 Requested listing

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
Populations 1 initial and continuing, grandfathering				
RISDIPLAM Powder for oral solution 60mg	3	5	\$32,573.49 private published price \$32,525.67 public published price	EVRYSDI® Roche
Population 2 and 3 – initial				

Public Summary Document - March 2023 PBAC Meeting

RISDIPLAM Powder for oral solution 60mg	1	0	\$10,899.71 private published price \$10,841.89 public published price	EVRYSDI®	Roche
<b>Condition:</b>	Spinal muscular atrophy				
<b>PBS Indication:</b>	Treatment of spinal muscular atrophy				
<b>Restriction:</b> Section 100 (Highly specialised drugs program)	<input checked="" type="checkbox"/> Authority Required - In Writing (for initial therapy) <input checked="" type="checkbox"/> Authority Required – Telephone (for continuing therapy)				
<b>Treatment criteria:</b>	Must be treated by a specialist medical practitioner experienced in the diagnosis and management of SMA associated with a neuromuscular clinic, or in consultation with a specialist medical practitioner experienced in the diagnosis and management of SMA associated with a neuromuscular clinic				
<b>For initial therapy</b>	<p><u>All populations</u>            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 treatment must be given concomitantly with best supportive care for this condition, but this benefit is the sole PBS-subsidised disease modifying treatment.            AND            The treatment must not be in combination with other disease modifying treatments for this condition</p> <p><u>Population 1</u>            Patient must be at least 19 years of age at the time of this authority application, but never claimed PBS subsidy for a disease modifying treatment during childhood            AND            Patient must have SMA where the onset of signs/symptoms (at least one) of SMA first occurred prior to their 19th birthday (SMA symptom onset after this age will be considered type IV SMA, which is not PBS-subsidised).</p> <p><u>Population 2 and 3</u>            The condition must have genetic confirmation that there are 1 to 3 copies of the survival motor neuron 2 (SMN2) gene            AND            The condition must be pre-symptomatic            AND            Patient must be untreated with gene therapy            AND            Patient must be aged under 36 months prior to commencing treatment.</p> <p><u>Grandfathering</u>            Patient must have previously received treatment with this drug for this condition prior to [PBS listing date]</p>				
<b>For continuing therapy</b>	<p><u>All populations</u>            Patient must be undergoing concomitant treatment with best supportive care, but this benefit is the sole PBS-subsidised disease modifying treatment            AND            Patient must not be receiving invasive permanent assisted ventilation in the absence of a potentially reversible cause while being treated with this drug.</p> <p><u>Population 1</u>            Patient must be undergoing continuing PBS-subsidised treatment that was initiated through the Initial treatment listing for SMA initiated in adulthood.            AND            The treatment must be each of: (i) occurring from week 104 onwards relative to the first administered dose, (ii) demonstrating a clinically meaningful response;            OR</p>				

	<p>The treatment must be occurring within the first 104 weeks from the first administered dose</p> <p><u>Population 2 and 3 (as amendment to existing listing for continuing treatment with risdiplam)</u>          Continuing/maintenance treatment of either symptomatic Type I, II or III SMA, or of a patient commenced on this drug under the pre-symptomatic SMA listing</p>
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Source: Table 1.9, p30, table 1.10, p31, table 1.11, p32, table 1.12, p33, table 1.13, p34, table 1.14, p37 and table 1.15, p38 of the resubmission

- 3.1 The resubmission requested a Special Pricing Arrangement (SPA) and proposed an in-principle agreement that the effective price of risdiplam will be no higher than the cost-minimised effective price for nusinersen in populations 1 and 2.
- 3.2 The resubmission proposed that continuation of treatment in pre-symptomatic patients in population 2 (and 3) would fall under an amended listing of the existing continuation PBS listing for risdiplam.
- 3.3 Under the current PBS-listing and the proposed PBS populations in this resubmission, SMA patients currently aged between 3 and 18 years who did not exhibit symptoms until between age 3 to 18 years (i.e. Type 3b/c) would not be able to access risdiplam until age 19. This may cause a potential equity issue (see paragraph 2.5 above).
- 3.4 The proposed restrictions for population 1 (adult initiation) were consistent with the existing restrictions for nusinersen in this population with the exception of:
  - Inclusion of the criterion requiring treatment is by a specialist medical practitioner experienced in the diagnosis and management of SMA associated with a neuromuscular clinic, or in consultation with a specialist medical practitioner experienced in the diagnosis and management of SMA associated with a neuromuscular clinic. The related restriction for nusinersen is: Must be treated by a specialist medical practitioner experienced in the diagnosis/management of SMA; OR Must be treated by a medical practitioner who has been directed to prescribe this benefit by a specialist medical practitioner experienced in the diagnosis/management of SMA.
  - Criteria relating to loading doses (this was appropriate).
  - The continuing restriction included additional population criteria not required for the continuing listing (at least 19 years of age, signs/symptoms prior to 19 years).
- 3.5 The proposed restrictions for population 2 (paediatric pre-symptomatic initiation 1-2 copies SMN2) were consistent with the existing initial and continuing restrictions for nusinersen in this population with the exception of criteria relating to loading doses (this was appropriate).
- 3.6 The PBAC considered that the wording of the initial listing should be amended such that Grandfather patients are eligible to access risdiplam via the proposed initial and continuing listings, making a separate listing unnecessary.

*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*. Patients with milder forms of SMA usually have higher *SMN2* copy numbers than severe SMA patients.

4.2 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. SMA can be classified into several clinical subtypes based on age of onset and severity of the disease, as detailed in Table 2. Type 3 patients can be further classified depending on age at symptom onset, with Type 3a patients being 18 months-3 years at disease onset.

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

SMA Type	Age at symptom onset	Able to sit	Able to stand	Able to walk	Typical symptoms	Life expectancy	Typical <i>SMN2</i> copy number <sup>c</sup>	Population included in proposed PBS listing
0	Prenatal	X	X	X	Severe hypotonia <sup>b</sup>	Death in weeks	1	X
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	3-4	✓
3b <sup>a</sup>	>3 years	✓	✓	Assisted	Later loss of ambulation			✓ <sup>d</sup>
4	>18 years	✓	✓	✓	Slow, progressive muscle weakness. Ambulant until later in life.	Normal	4, 5, 6	X

Source: Table 1.2 (p5) of the resubmission

PBS = pharmaceutical benefits scheme; SMN = survival motor neuron

a - Recent publications also distinguish between Type 3b and 3c SMA, with Type 3c SMA being defined as when symptoms develop after 12 years but before 19 years of age

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. *SMN2* copy number does not define SMA Type, and there is some patient variability in *SMN2* copy number within SMA Type.

d – However, Type 3b patients who are currently aged between 3 and 18 would not be eligible for risdiplam under the current and proposed risdiplam PBS-listing. Patients who would become Type 3b patients (i.e., first exhibit symptoms between the age of 3 and 18) would only be eligible for risdiplam if identified as pre-symptomatic through genetic testing and aged under 36 months (i.e., populations 2 or 3 of the submission).

4.3 Population 1, as targeted in the resubmission, does not include a requirement for patients to be a particular SMA Type. However, almost all patients in population 1 are likely to be either Type 2 or Type 3 SMA as there are currently approximately only 5

living adult Type 1 SMA patients in Australia, and Type 4 SMA, by definition, is only diagnosed if symptom-onset is after age 18.

- 4.4 The targeting of pre-symptomatic patients aged under 36 months in populations 2 and 3 aligns with the under 36-month age criteria for the current nusinersen pre-symptomatic SMA PBS-listing. The PBAC has previously considered that pre-symptomatic initiation of SMA treatment should be limited to patients less than three years of age (para 7.9, nusinersen PSD, July 2020 PBAC meeting) and ESC has previously noted it would be impractical to limit pre-symptomatic initiation to patients under 6 weeks given current SMA screening procedures (para 2.3, nusinersen PSD, July 2020 PBAC meeting).
- 4.5 Risdiplam, an *SMN2* pre-mRNA splicing modifier, is an orally administered DMT for the treatment of SMA. Functional SMN protein deficiency is the pathophysiological mechanism of all SMA types, therefore the need to systemically increase SMN protein is at the core of disease interventions across the continuum of SMA phenotypes. Risdiplam corrects the splicing of *SMN2* to shift the balance from exon 7 exclusion to exon 7 inclusion into the mRNA transcript. This leads to a sustained increase in the expression of functional SMN protein from the *SMN2* gene. Risdiplam crosses the blood-brain barrier and thereby results in an increase in SMN protein in both the CNS and the periphery, whereas nusinersen results in an increase in SMN protein in the CNS only.

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

## **5 Comparator**

- 5.1 For population 1, the resubmission appropriately nominated nusinersen as the comparator. Nusinersen is the only PBS-listed therapy for patients aged  $\geq 19$  with  $\geq 1$  SMA symptom experienced before the age of 19.
- 5.2 For population 2, the resubmission appropriately nominated nusinersen as the main comparator. Nusinersen is PBS-listed for pre-symptomatic patients aged  $< 36$  months-old with 1 or 2 copies of the *SMN2* gene. ONA is also PBS-listed for pre-symptomatic patients aged  $< 9$  months-old with 1 or 2 copies of the *SMN2* gene. This population is applicable to the subset of patients in population 2 who are aged  $< 9$  months in the current resubmission. The resubmission provided the following justifications for nominating nusinersen as the main comparator:
- Whilst both nusinersen and ONA are PBS-listed for this indication, ONA is only listed for patients aged  $< 9$  months of age whereas nusinersen is listed for patients aged  $< 36$  months of age;
  - During the previous risdiplam submission, the PBAC recommended that risdiplam should be treated as interchangeable on an individual patient basis with nusinersen (para 7.11, risdiplam PSD, March 2021 PBAC meeting). During its September 2021 PBAC consideration for ONA, the PBAC considered that ONA

should not be treated as interchangeable on an individual patient basis with any other drug (para 9.18, ONA PSD, September 2021 PBAC meeting); and

- Nusinersen has been listed on the PBS for this population since December 2020, whilst ONA has been listed since May 2022.

- 5.3 The resubmission did not present a comparison to ONA in population 2. However, based on clinician feedback from a 2022 pre-symptomatic SMA advisory board, 60.8% of patients may be treated with ONA pre-symptomatically.
- 5.4 For population 1, the proposed clinical management algorithm for risdiplam appropriately considered risdiplam could be used in place of nusinersen, but not in combination.
- 5.5 For population 2, the proposed clinical management algorithm for risdiplam appropriately considered that risdiplam could be used in place of nusinersen or ONA, but not in combination. However, the resubmission inappropriately only considered the replacement of nusinersen in the population 2 financial estimates.

*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 (22), via the Consumer Comments facility on the PBS website. Regarding population 1, patients currently accessing risdiplam described observed improvements in breathing and swallowing, as well as increased energy, mobility, strength, dexterity, and flexibility. Patients also described an increase in independence, aided by the opportunity for self-administration of treatment, as well as an ability to eat without feeding tubes, communicate verbally, and continue to work. Regarding both populations 1 and 2, individuals who would like to access risdiplam and their carers noted that it would provide a less invasive and more convenient treatment option, noting also that not all patients are suitable for intrathecal administration of nusinersen.

### ***Clinical studies***

- 6.3 For population 1, the resubmission was based on naïve (unanchored) numerical comparisons between risdiplam and nusinersen. The adult subgroup from two risdiplam studies (SUNFISH part 2, referred to as SUNFISH herein & JEWELFISH) provided the clinical data for risdiplam and two nusinersen studies (Hagenacker 2020, Maggi 2020) and the adult subgroup of one nusinersen study (Pera 2021) provided the clinical data for nusinersen. The resubmission additionally considered one single-arm observational risdiplam study (Garzon 2022; n=6), and six real-world evidence

nusinersen studies, as supportive evidence. However, no data from these supportive evidence studies were used in the naïve indirect comparisons, and no safety data from these studies were presented.

- 6.4 For population 2, the resubmission presented naïve (unanchored) numerical comparisons between risdiplam and nusinersen. These comparisons were informed by the two *SMN2* gene copy number subgroups of one risdiplam study (RAINBOWFISH) and one nusinersen study (NURTURE).
- 6.5 The PBAC has previously considered earlier data-cuts of the SUNFISH, JEWELFISH and NURTURE trials compared to the data-cuts presented in the current resubmission. The PBAC has also previously considered results from Maggi 2020 and Hagenacker 2020. The PBAC has not previously considered results from Pera 2021, however has previously considered data pooled from three European SMA registries (para 6.6, nusinersen PSD, July 2021 PBAC meeting) and there may be some overlap of patients in the SMA registry previously considered with those enrolled in Pera 2021. The PBAC has not previously considered RAINBOWFISH.
- 6.6 Details of the studies presented in the resubmission that were used to inform the clinical claims are provided in Table 3.

**Table 3: Studies and associated reports presented in the resubmission**

Study ID	Protocol title/ Publication title	Publication citation
<b>Risdiplam studies – Adult SMA population (Population 1)</b>		
SUNFISH	A Two-Part Seamless, Multi-Centre Randomized, Placebo-Controlled, Double-blind Study To Investigate The Safety, Tolerability, Pharmacokinetics, Pharmacodynamics And Efficacy Of Ro7034067 In Type II And III Spinal Muscular Atrophy Patients	Primary Report Feb 20 Report no. 1099250 (SUNFISH PRIMARY CSR 2020); June 20 Update Report no. 1101749 (SUNFISH Update CSR 2020); March 21 Update Report no. 1105946 (SUNFISH Update CSR 2021); Clinical Appendix
	Mercuri E et al. Safety and efficacy of once-daily risdiplam in type II and non-ambulant type III spinal muscular atrophy (SUNFISH Part 2): a phase 3, double-blind, randomised, placebo-controlled trial.	<i>Lancet Neurol.</i> 2022;21(1):42-52
	Deconinck, N. et al. SUNFISH: 3-year Efficacy and Safety of Risdiplam in Types 2 and 3 Spinal Muscular Atrophy.	<i>Journal of Neuromuscular Diseases.</i> 2022;PS06.01(9):S112-S13
	Goemans, N. et al. SUNFISH: 3-year efficacy and safety of risdiplam in Types 2 and 3 spinal muscular atrophy	<i>European Journal of Neurology.</i> 2022;29(278)
	Baranello, G. et al. SUNFISH PART 2: 24-Month Efficacy And Safety Of Risdiplam In Type 2/3 SMA	<i>Journal of Neurology, Neurosurgery and Psychiatry.</i> 2022b;93(95-96)
	Servais, L et al. SUNFISH PART 2: Risdiplam In Type 2 And Type 3 SMA.	<i>Journal of Neurology, Neurosurgery and Psychiatry.</i> 2022c;93(A87)

Public Summary Document - March 2023 PBAC Meeting

Study ID	Protocol title/ Publication title	Publication citation
<b>Risdiplam studies – Adult SMA population (Population 1)</b>		
JEWELFISH	An Open-Label Study To Investigate The Safety, Tolerability, And Pharmacokinetics/Pharmacodynamics Of Ro7034067 In Adult And Paediatric Patients With Spinal Muscular Atrophy	JEWELFISH Update CSR 2021, Clinical Appendix
<b>Nusinersen studies – Adult SMA population (Population 1)</b>		
Maggi 2020	Maggi, L. et al. Nusinersen safety and effects on motor function in adult spinal muscular atrophy type II and III.	<i>Journal of Neurology, Neurosurgery and Psychiatry</i> 2020;91(11):1166-1174
Hagenacker 2020	Hagenacker, T et al. Nusinersen in adults with 5q spinal muscular atrophy: a non-interventional, multicentre, observational cohort study	<i>The Lancet Neurology</i> 2020; 19(4),317-325
Pera 2021	Pera, M. et al. Nusinersen in pediatric and adult patients with type III spinal muscular atrophy.	<i>Ann Clin Transl Neurol.</i> 2021;8(8):1622-34
<b>Risdiplam studies – Pre-symptomatic SMA population (Populations 2 and 3)</b>		
RAINBOWFISH	Interim CSR Study BN40703, (RAINBOWFISH) An Open-Label Study Of Risdiplam In Infants With Genetically Diagnosed And Presymptomatic Spinal Muscular Atrophy	Report No. 1109915 2021; October 2021 (Clinical Appendix)
	Servais, L. et al. A study of risdiplam in infants with presymptomatic spinal muscular atrophy (SMA).	<i>Developmental Medicine and Child Neurology.</i> 2022;Poster presentation, volume 64(71)
	Servais, L. et al. Preliminary Efficacy and Safety Data in Risdiplam-Treated Infants with Presymptomatic Spinal Muscular Atrophy.	<i>Journal of Neuromuscular Diseases.</i> 2022b;9:S114-S15
	Finkel, R. et al. Preliminary Efficacy and Safety Data in Risdiplam-Treated Infants with Presymptomatic SMA.	<i>Neurology.</i> 2022;98.
<b>Nusinersen studies – Pre-symptomatic SMA population (Population 2)</b>		
NURTURE	De Vivo, D. et al. Nusinersen initiated in infants during the presymptomatic stage of spinal muscular atrophy: Interim efficacy and safety results from the Phase 2 NURTURE study.	<i>Neuromuscul Disord.</i> 2019;29(11):842-56
	Crawford, T et al. Effect in Infants in the Presymptomatic Stage of SMA: 4.9-year Interim of the NUTURE Study	MDA (2022) Muscular Dystrophy Association - 4th Clinical and Scientific Conference. 2022;March 13-16, 2022, Nashville, TN(Abstract presentation)
	Kirschner, J. et al. Impact of Nusinersen on Caregiver Experience and HRQoL in Presymptomatic SMA: NURTURE Study Results	<i>Journal of Neuromuscular Diseases.</i> 2022;9:S113-S14.
	Strauss, K. et al. Onasemnogene abeparvovec for presymptomatic infants with three copies of SMN2 at risk for spinal muscular atrophy: the Phase III SPR1NT trial	<i>Nat Med.</i> 2022b;28(7):1390-97

Source: Tables 2.4 and 2.5 (p53-4) of the resubmission)

SMA = spinal muscular atrophy

6.7 The key features of the included evidence are summarised in Table 4.

**Table 4: Key features of the included evidence**

Study	N	Design/ duration	Risk of bias <sup>c</sup>	Patient population	Outcomes
<b>Population 1 (adult population) – risdiplam</b>					
SUNFISH Part 1	51	Phase 3, MC, R, DB, PC, 2 years <sup>a</sup>	Low	2-25 years-old, Type 2 or 3 SMA, ambulant or non-ambulant	Safety, tolerability, PK and PD
SUNFISH Part 2	180	Phase 3, MC, R, DB, PC, 5 years, ongoing <sup>a</sup>	Low	2-25 years-old, Type 2 or non-ambulant Type 3 SMA	MFM32, HFMSE, RULM
JEWELFISH	174	Phase 2, MC, Exploratory, NC, OL, single-arm, 5 years, ongoing	High	6 months-60 years-old; Type 1-3 SMA, previously-treated	MFM32, HFMSE, RULM, 6MWT
<b>Population 1 (adult population) – nusinersen</b>					
Maggi 2020	116	Retrospective cohort, single-arm, 14 months	High	Type 2 or 3 SMA, nusinersen initiation >17 years-old	HFMSE, RULM, 6MWT
Hagenacker 2020	124	Prospective, observational cohort, single-arm, 14 months	High	16-65 years-old, SMA	HFMSE, RULM, 6MWT
Pera 2021	67	International registry, 12 months	High	Type 3 SMA, on nusinersen for ≥12 months	HFMSE, RULM, 6MWT
<b>Population 2 and 3 (pre-symptomatic population) – risdiplam</b>					
RAINBOWFISH	18	Phase 2, MC, OL, single-arm, 5 years, ongoing	High	≤6 weeks-old, pre-symptomatic, genetically-diagnosed SMA	OS, event-free survival, HINE-2, CHOP-INTEND, BSID-III
<b>Population 2 (pre-symptomatic population) – nusinersen</b>					
NURTURE	25	Phase 2, MC, OL, single-arm, 5 years, ongoing	High	≤6 weeks-old, pre-symptomatic, genetically-diagnosed SMA, 2 or 3 SMN2 gene copies	OS, event-free survival, HINE-2, CHOP-INTEND

Source: Section 2.3 (p58-76 of the resubmission)

DB = double blind; GMFM = Gross Motor Function Measure; HFMS=Hammersmith Functional Motor Scale; HFMSE=Hammersmith Functional Motor Scale– Expanded; 6MWT=6 min walking test; NR=not reported; MFM32=motor function measure 32; MVICT = Maximal Voluntary Isometric Muscle Contraction Testing; MC = multicentre; NC = non-comparative; PC = placebo-controlled; OL = open-label; OS = overall survival; R = randomised; RULM=Revised Upper Limb Module; SMA=spinal muscular atrophy, SMAFRS = modified SMA function rating scale; ULM = Upper Limb Module

Blue shaded cells indicate trials previous considered by PBAC, but at an earlier data cut or different subgroup for SUNFISH part 2, JEWELFISH and NURTURE

a – Only the first part was double-blinded and placebo-controlled. SUNFISH Part 1 was a dose-finding study whereby an open-label extension component of the pivotal risdiplam dosage followed the initial blinded placebo-controlled dose-finding component.

b – Only the first 12 months of SUNFISH 2 was placebo-controlled. After this placebo patients switched to risdiplam in a blinded manner for 12 months. Following this was a 3-year open-label extension component

c – All studies other than SUNFISH were single-arm, open-label, non-comparative studies and therefore considered as high risk of bias

### Population 1 – adult population

6.8 SUNFISH enrolled SMA patients aged 2-25 years with Type 2 and non-ambulant Type 3 SMA. The requested population includes all adults with Types 1-3, including Type 3 ambulant patients. The PBAC has previously noted these heterogeneity issues in the requested adult population (para 6.28, risdiplam PSD, March 2021 PBAC meeting). JEWELFISH enrolled patients aged 6 months to 60 years who have previously had DMT treatment for SMA, with any Type of SMA. These criteria were inconsistent with the requested population which required patients to have had no previous treatment with a DMT, and restricted use only to patients aged above 19 years and symptom onset prior to 18 years of age (i.e. Type 1-3 SMA). Only data from patients aged 18 years and above were used to inform the clinical comparison.

- 6.9 The nusinersen studies used to inform population 1 were real-world studies (single-arm retrospective/prospective cohort studies and registry data) and had eligibility criteria which were less restrictive than in SUNFISH and JEWELFISH. There was a notable degree of heterogeneity across the risdiplam and nusinersen studies with respect to age, ambulation status, previous treatment, degree of disease progression and extent of baseline function, as previously noted for the nusinersen studies (para 6.34 and 7.08, nusinersen PSD, March 2022 PBAC meeting). Mean baseline Hammersmith Functional Motor Scale (HFMSE) scores in the primary nusinersen studies (24-29) were substantially higher than in the risdiplam studies, (9-10) with a correspondingly lower proportion with scoliosis (14-25% vs 85-93%) and lower proportion with Type 2 SMA (0-35% vs more than 50%). Additionally, there were notable differences in the timing of outcome assessments. This caused a large degree of uncertainty in the interpretation of all naïve comparisons between the studies.
- 6.10 None of the studies included any adjustments for multiple testing from measuring the outcome at several timepoints. In SUNFISH part 2, the primary outcome was change from baseline in the motor function measure (MFM32) at 12 months and all other outcomes relied upon by the submission were considered exploratory outcomes. All efficacy outcomes in JEWELFISH were also considered exploratory.
- 6.11 Follow-up in both risdiplam and nusinersen studies was limited, with a maximum follow-up of 24 months in the risdiplam studies and a maximum follow-up of 14 months in the nusinersen studies. Given the lifelong nature of SMA, this represents an important area of uncertainty in regard to long-term treatment benefit associated with both risdiplam and nusinersen.
- 6.12 The HFSME and Revised Upper Limb Module (RULM) outcome measures in the adult subgroups were used to undertake efficacy comparisons in population 1. The PBAC has previously considered these outcomes and has noted that recent publications suggest the HFMSE and RULM may not be meaningful outcome measures for severely affected individuals (para 7.4, nusinersen PSD, July 2021 PBAC meeting).
- 6.13 The HFMSE contains a series of assessments designed to assess important functional abilities, including standing, transfers, ambulation, and proximal and axial function. The HFMSE total score scale contains 33 items, which are scored on a 3-point Likert-type scale (0–2) and summed to derive the total score, with lower scores indicating greater impairment.
- 6.14 The RULM test is an outcome measure specifically developed to assess upper limb functional abilities in SMA patients. The test assesses important aspects of upper limb function. Items are scored either 0, 1 or 2, with 0 indicating cannot complete the task independently and, 1 can complete independently with a modified method, and 2 completes task without assistance. The total score ranges from 0 to 37 with higher scores indicating greater functional abilities.
- 6.15 The resubmission did not nominate minimal clinically important differences (MCIDs) for these outcomes, noting a lack of published non-inferiority margins in SMA and

given the lack of precision in the confidence estimates for the naïve comparisons due to small study population. The resubmission also noted that information from patient and clinician focus groups conducted at the beginning of 2022 for the nusinersen PBAC resubmission considered that changes in scores from these outcome measures should not be used in isolation to determine treatment effectiveness. ESC has previously considered the importance of these outcomes in terms of clinically meaningful benefit in adult patients was unclear (para 6.22, nusinersen PSD, March 2022 PBAC meeting). Without an established non-inferiority margin, it was unclear whether any claim of non-inferiority would be robust.

#### Population 2 - pre-symptomatic 1-2 SMN2 gene copies

- 6.16 RAINBOWFISH and NURTURE enrolled patients aged  $\leq 6$  weeks. Under the requested restrictions any patient aged  $< 36$  months would be eligible for treatment. RAINBOWFISH did not enrol patients based on SMN2 gene copy number and neither trial enrolled any patients with one copy of the SMN2 gene. As such, only 7/18 (39%) of patients who had  $\leq 2$  SMN2 gene copies were applicable to the requested population. NURTURE enrolled patients with two (n=15, 60%) and three (n=10) copies of SMN2 only.
- 6.17 RAINBOWFISH patients had slightly lower motor functioning scores than NURTURE patients at baseline, but it was unclear if this difference was meaningful as the standard deviations of all measures were large due to the small sample sizes. Additionally, the subgroup of patients with two copies of the SMN2 gene had a sample size of only 7 patients in RAINBOWFISH and 15 in NURTURE.
- 6.18 In population 2 the clinical comparison was based on outcomes of event-free survival, overall survival, Hammersmith Infant Neurological Exam (HINE)-2 total score change from baseline, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) total score change from baseline and individual motor milestones. The PBAC has previously considered CHOP-INTEND and HINE-2 at the March 2021 PBAC meeting (risdiplam).
- 6.19 The HINE was developed to assess neurological function for infants. Specifically, the HINE-2 consists of 8 items that assess incremental changes in head control, sitting, voluntary grasp, ability to kick, rolling, crawling, standing, and walking. The HINE module is shorter and includes less items of the motor component of the Bayley Scales on Infant and Toddler Development that includes many items that are not relevant to Type I SMA.
- 6.20 The CHOP-INTEND was designed to measure motor function in weak infants with neuromuscular disease. The CHOP-INTEND is a physical therapy assessment designed for, validated, and shown to be reliable in SMA Type I. CHOP-INTEND 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 achievement and maintenance of scores  $> 40$  points are considered to be clinically meaningful because

patients with SMA Type I rarely achieve and never maintain this level of motor function.

- 6.21 The resubmission did not nominate MCIDs for these outcomes due to uncertainty around the magnitude of incremental benefit from pre-symptomatic initiation of treatment compared with symptomatic treatment, which remains an outstanding issue without new clinical data (para 6.17 and 7.03, nusinersen PSD, July 2021). The resubmission also did not nominate non-inferiority thresholds for these outcomes and without an established non-inferiority margin it was unclear whether any claim of non-inferiority would be robust.

### Comparative effectiveness

#### Population 1 (adult population)

- 6.22 Due to the lack of direct comparative trials of risdiplam versus nusinersen, or trials with a common comparator arm, the resubmission presented naïve numerical comparisons of risdiplam versus nusinersen in the adult population.
- 6.23 Table 5 presents the HFMSE mean change from baseline adult subgroup results used to inform the naïve numerical comparisons.

Table 5: HFMSE mean difference versus baseline in studies used for naïve numerical comparison

	HFMSE Total Score	HFMSE difference versus baseline				
	Baseline	Month 6	Month 10	Month 12	Month 14	Month 24
<b>SUNFISH Part 2 (18-25 years)</b>						
N	14	-	-	14	-	10
Mean (SD)	9.79 (9.45)	-	-	-0.64 (1.69)	-	-0.50 (3.50)
95% CI	(4.33, 15.24)	-	-	(-1.62, 0.33)	-	(-3.01, 2.01)
<b>JEWELFISH (≥18 years)</b>						
N	62	-	-	52	-	46
Mean (SD)	9.02 (12.40)	-	-	0.35 (1.94)	-	0.37 (1.96)
Median	4.0	-	-	0	-	0
95% CI	(5.87, 12.17)	-	-	(-0.19, 0.89)	-	(-0.21, 0.95)
p-value		-	-	0.20	-	0.21
<b>Hagenacker 2020<sup>a</sup> (Nusinersen primary study)</b>						
N <sup>a</sup>	173	124	92	-	57	-
Mean (SD)	23.85 (12.16)	1.73 (NR)	2.58 (NR)	-	3.12 (NR)	-
Median	NR	NR	NR	-	NR	-
95% CI	NR	(1.05, 2.41)	(1.76, 3.39)	-	(2.06, 4.19)	-
<b>Maggi 2020 (Nusinersen primary study)</b>						
N	116	116	84	-	51	-
Mean (SD)	26.5 (21.7)	1.33 (2.29)	2.29 (2.75)	-	2.69 (2.92)	-
Median	22.5	1	1	-	2	-
Range	(0, 64)	(-5, 8)	(-3, 9)	-	(-3, 11)	-
<b>Pera 2021 (Nusinersen primary study) (adult subgroup)</b>						
N	45	-	-	45	-	-
Mean (SD)	30.75 (NR)	-	-	0.79 (NR)	-	-
IQR	(29.97, 31.53)	-	-	(0.29, 1.87)	-	-

Source: Tables 2.24, 2.27 and 2.30 of the resubmission (p94-8); JEWELFISH 'Adult subgroup – eff\_jewelfish\_2y\_chg'.pdf  
 CI=confidence interval; HFMSE= Hammersmith Functional Motor Scale – Expanded; SD=Standard deviation; n=number of patients  
 a - Included patients aged 16-65 years old  
 Blue shaded cells indicate trials previously considered by PBAC

- 6.24 The sample sizes in SUNFISH Part 2 were small (n=14 at month 12 and n=10 at week 24). The only comparable result with respect to timing of assessment post-baseline between risdiplam and nusinersen studies was at month 12 for SUNFISH Part 2 and JEWELFISH versus Pera (2021).
- 6.25 Overall, it was likely reasonable to conclude that adult patients treated with nusinersen did not experience any decline in HFMSE function at up to 14 months of treatment based on the point estimates, though the magnitude of improvement (if any) was highly uncertain. Comparatively, adult patients treated with risdiplam experienced no change or minor decline in HFMSE function at up to 24 months of follow-up based on the point estimates, and any improvement over time was of a smaller magnitude than reported in the primary nusinersen studies. However, the clinical significance of any difference was highly uncertain given the numerous heterogeneity issues between the included studies.
- 6.26 Table 6 presents the RULM mean change from baseline adult subgroup results used to inform the naïve numerical comparisons.

**Table 6 RULM mean difference versus baseline in studies used for naïve numerical comparison**

	RULM Total Score	RULM difference versus baseline				
	Baseline	Month 6	Month 10	Month 12	Month 14	Month 24
<b>SUNFISH Part 2 (18-25 years) - RISDIPLAM</b>						
N	14	-	-	14	-	10
Mean (SD)	18.21 (6.59)	-	-	1.29 (2.13)	-	1.50 (2.88)
95% CI	(14.41, 22.02)	-	-	(0.06, 2.51)	-	(-0.56, 3.56)
<b>JEWELFISH (≥18 years) - RISDIPLAM</b>						
N	62	-	-	52	-	47
Mean (SD)	15.11 (9.50)	-	-	-0.50 (2.97)	-	0.17 (2.80)
Median	16	-	-	0	-	0
95% CI	(12.70, 17.53)	-	-	(-1.31, 0.31)	-	(-0.65, 0.99)
<i>p-value</i>		-	-	0.22	-	0.68
<b>Hagenacker 2020 <sup>a</sup> - NUSINERSEN</b>						
N	173	120	90	-	58	-
Mean (SD)	20.87 (13.27)	0.66 (NR)	0.59 (NR)	-	1.09 (NR)	-
Median	NR	NR	NR	-	NR	-
95% CI	NR	(0.26, 1.05)	(0.15, 1.03)	-	(0.62, 1.55)	-
<b>Maggi 2020 - NUSINERSEN</b>						
N	116	114	80	-	49	-
Mean (SD)	25.22 (11.63)	0.37 (1.97)	0.72 (2.07)	-	0.94 (2.13)	-
Median	29	0	0	-	1	-
Range	(0, 37)	(-8, 6)	(-6, 6)	-	(-6, 6)	-
<b>Pera 2021 (adult subgroup) - NUSINERSEN</b>						
N	55	-	-	55	-	-
Mean (SD)	27.31 (NR)	-	-	0.07 (NR)	-	-
IQR	(26.91, 27.71)	-	-	(-0.48, 0.63)	-	-

Source: Tables 2.24, 2.27, 2.30 and 2.39 of the resubmission (p94-8 & 116); JEWELFISH 'Adult subgroup – eff\_jewelfish\_2y\_chg' pdf  
 CI=confidence interval; RULM= Revised upper limb module; SD=Standard deviation; n=number of patients  
 a – Included patients aged 16-65 years old

- 6.27 In the risdiplam studies, minor improvements (<1.5 points change) as measured by mean changes in RULM from baseline were reported in patients treated with

risdiplam, except for JEWELFISH at month 12, which was a minor decrease. In the nusinersen studies, minor improvements (<1.0 points change) as measured by mean changes in RULM from baseline were similarly reported in patients treated with nusinersen. Overall, the magnitude of mean change from baseline in RULM was numerically similar for the included risdiplam studies and the nusinersen studies when comparing point estimates, though there was high uncertainty in this comparison due to the heterogeneity between studies.

**Population 2 (pre-symptomatic 1/2 SMN2 gene copy population)**

- 6.28 Due to the lack of direct comparative trials of risdiplam versus nusinersen, or trials with a common comparator arm, the resubmission presented naïve numerical comparisons of risdiplam versus nusinersen in the pre-symptomatic one or two SMN2 gene copy subgroup population.
- 6.29 The follow up in RAINBOWFISH (median 8.72 months and maximum 16.8 months) was substantially shorter than in NURTURE (median 34.8 months based on De Vivo 2019). The long-term development and clinical benefit of treatment of risdiplam in this population is uncertain given the short duration of follow-up in RAINBOWFISH.
- 6.30 All patients in the risdiplam RAINBOWFISH study (n=7) and nusinersen NURTURE study (n=15) with two copies of SMN2 had achieved overall survival and event-free survival (avoidance of permanent ventilation) at the end of follow-up.
- 6.31 Table 7 presents the change from baseline values in HINE-2 total score and the difference between studies in the two SMN2 gene copy patients.

**Table 7: HINE-2 total score RAINBOWFISH vs NURTURE in patients with 2 SMN2 gene copies**

		Risdiplam (n=7)	Nusinersen (=15)
Baseline		2.0	2.7
Change from baseline (SD):	Week 8/9.1*	0.83 (1.17)	2.38 (NR)
	Week 28/26.1*	10.80 (4.09)	9.80 (NR)
Difference in change from baseline values (Ris vs. Nus)	Week 8/9.1*	-1.55 (p-value<0.05)	
	Week 28/26.1*	1.00 (p-value = 0.61)	

Source: Table 2.42 (p118) of the resubmission

HINE-2= Hammersmith Infant Neurological Examination Module 2; Nus= Nusinersen; Ris= Risdiplam; NR= not reported; SD: Standard deviation

\*NURTURE assessment schedule differs to RAINBOWFISH; 9.1 and 26.1 weeks are referring to the NURTURE assessment time points. 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). The standard deviations for nusinersen were estimated from the Figures in De Vivo 2019 and an assumption was made that the populations were normally distributed.

- 6.32 At the week 8 (RAINBOWFISH) / week 9 (NURTURE) timepoint, risdiplam patients had a 1.55 point lower mean increase in HINE-2 total score from baseline than nusinersen patients, but at the week 28 (RAINBOWFISH) / week 26.1 (NURTURE) timepoint, risdiplam patients had a 1.00 point higher mean increase in HINE-2 total score from baseline than nusinersen patients. These conflicting results may be partially explained by the differences in timing of outcome assessment between trials. The p-values from these mean differences showed statistical significance at the 5% level for the week 8/9.1 timepoint, and no statistical significance for the week 28/26.1 timepoint, however these were post-hoc exploratory analyses. Pre-symptomatic patients with

two *SMN2* copy numbers treated with risdiplam and nusinersen achieved similar levels of HINE-2 score after 28 and 26.1 weeks of treatment, respectively.

6.33 Table 8 presents the results of motor milestone achievements, as measured by the HINE-2, in RAINBOWFISH and NURTURE two *SMN2* gene copy subgroups.

**Table 8: Individual motor milestone achievements RAINBOWFISH vs NURTURE in patients with 2 *SMN2* gene copies**

	RAINBOWFISH trial (n=7) Risdiplam (12 months follow-up)	NURTURE trial (n=15) Nusinersen (34.8 months follow-up)
Sitting independently (%)	N=4 4 (100)	N=15 15 (100)
Standing independently (%)	N=4 1 (25)	N=15 9 (60)
Walking independently (%)	N=4 1 (25)	N=15 13 (87)

Source: Table 2.2.44 (p119) of the resubmission

Motor milestones were measured by the Hammersmith Infant Neurological Examination – Module 2(HINE-2) in the RAINBOWFISH and NURTURE trials

6.34 NURTURE had a notably longer median follow-up compared to RAINBOWFISH. This substantially impacts the comparability of results in favour of nusinersen as paediatric patients would naturally have further development over a longer period of time. Additionally, only 4/7 (57%) RAINBOWFISH patients had data at 12 months for this outcome, further increasing uncertainty. The results show all patients in both trials had achieved the ability to sit-up independently, but a higher proportion of NURTURE patients had achieved the ability to stand independently (60% vs 25%) and walk independently (87% vs 25%) than RAINBOWFISH patients.

6.35 Table 9 presents the difference in change from baseline values in CHOP-INTEND total score between studies in the two *SMN2* gene copy subgroups.

**Table 9: CHOP-INTEND total score RAINBOWFISH vs NURTURE in patients with 2 *SMN2* gene copies**

		Risdiplam (n=7)	Nusinersen (n=15)
Baseline		44.43	46.97
Change from baseline (SD):	Week 8/9.1*	5.8 (3.27)	4.62 (NR)
	Week 28/26.1*	14.6 (6.58)	10.99 (NR)
Difference in change from baseline values (Ris vs. Nus)	Week 8/9.1*	1.18 (p-value = 0.47)	
	Week 28/26.1*	3.61 (p-value = 0.29)	

Source: Table 2.43 (p119) of the resubmission

HINE-2= Hammersmith Infant Neurological Examination Module 2; Nus= Nusinersen; Ris= Risdiplam; NR= not reported; SD: Standard deviation

\*NURTURE assessment schedule differs to RAINBOWFISH; 9.1 and 26.1 weeks are referring to the NURTURE assessment time points. 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). The standard deviations for nusinersen were estimated from the Figures in De Vivo 2019 and an assumption was made that the populations were normally distributed.

6.36 The results show at the week 8/9.1 timepoint, patients treated with risdiplam had a 1.18 point higher mean increase in CHOP-INTEND total score from baseline than nusinersen patients, and at the week 28/26.1 timepoint a 3.61 point higher mean increase in CHOP-INTEND total score from baseline than nusinersen patients. The p-values for both comparisons were not statistically significant (i.e. >0.05), however, as

with the HINE-2 total score comparison, these p-values should be considered uncertain as post-hoc exploratory analyses.

### Comparative harms

#### Population 1 (adult population)

- 6.37 There was limited information on the comparative harms for risdiplam and nusinersen as no head-to-head clinical trials were identified.
- 6.38 The resubmission presented safety data for risdiplam in the adult subgroup of SUNFISH and JEWELFISH. Total trial safety data for SUNFISH has previously been considered at the March 2021 PBAC meeting, where the safety data for risdiplam was considered in comparison to placebo.
- 6.39 Table 10 presents an overview of adverse events (AEs) in the adult subgroups of SUNFISH and JEWELFISH.

**Table 10: Overview of adverse events in adult SMA patients in SUNFISH and JEWELFISH (safety population)**

Adverse event	Number of patients (%)	
	SUNFISH N=22 <sup>a</sup>	JEWELFISH N=63
Total number of patients with at least one AE	13 (59.1%)	17 (27.0%)
Total number of AEs	133	37
Total number of deaths	0	0
Total number of patients withdrawn from study due to an AE	0	NR
Total number of patients with at least one:		
AE with fatal outcome	0	0
Serious AE	1 (4.5%)	0
Serious AE leading to withdrawal from treatment	0	NR
Serious AE leading to dose modification/interruption	1 (4.5%)	NR
Treatment Related Serious AE	0	NR
AE leading to withdrawal from treatment	0	NR
AE leading to dose modification/interruption	1 (4.5%)	NR
Treatment related AE	2 (9.1%)	NR
Related AE leading to withdrawal from treatment	0	NR
Related AE leading to dose modification/interruption	0	NR
Grade 3-5 AE	1 (4.5%)	NR

Source: Table 2.48 (p121) of the resubmission

AE = adverse event; NR = not reported

- 6.40 Safety data for risdiplam patients in the adult subgroup of SUNFISH had a small sample size (n=14), and many AE variables in JEWELFISH were not reported in the adult subgroup, making it difficult to interpret risdiplam safety data specifically in the adult population. The results show 13/14 (93%) of SUNFISH patients experienced an AE, and one patient (7%) experienced a serious AE (SAE). However, 17 (27%) of JEWELFISH patients experienced an AE, and no patients experienced an SAE.
- 6.41 The resubmission noted safety data reported in the three primary nusinersen adult population studies. The PBAC has previously considered this data from Maggi 2020 and Hagenacker 2020. At its July 2021 meeting, the PBAC noted that AEs were

reported in 41.4% of patients in the Maggi 2020 study and in 47% of patients in the Hagenacker 2020 study. AEs relating to lumbar puncture were frequently observed with post-procedure headaches most commonly reported (Maggi 2020 37.1%; Hagenacker 2020 20%). Other administration-related adverse events such as lumbar puncture pain (Maggi 2020 8.6%) and back pain (Hagenacker 2020 9%) were also reported. Two patients in Maggi 2020 discontinued treatment after six months due to lack of subjective benefit and poor tolerability of repeated lumbar puncture. Two patients in Hagenacker 2020 withdrew from treatment due to drug related AEs (para 6.48, nusinersen PSD, July 2021 PBAC meeting).

Population 2 (pre-symptomatic 1/2 SMN2 gene copy population)

6.42 Table 11 presents an overview of total trial safety data in RAINBOWFISH and NURTURE.

**Table 11: Overview of adverse events in RAINBOWFISH and NURTURE**

	RAINBOWFISH <sup>a</sup> N=18 (%)	NURTURE N=25 (%)
Total number of patients with at least one AE	14 (77.8)	25 (100)
Total number of AEs	81	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	0	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 leading to withdrawal from treatment	0	0
AE leading to dose modification/interruption	2 (11.1)	NR
Treatment related AE	2 (11.1)	8 (32)
Related AE leading to withdrawal from treatment	0	0
Related AE leading to dose modification/interruption	0	NR
Grade 3-5 AE	2 (11.1)	17 (68)

Source: Table 2.51 (p124) of the resubmission

AE = adverse event; NR = not reported

a – includes 4 SMN2 four copy patients

6.43 In the total trial populations, all nusinersen patients experienced an AE, compared to 78% (14/18) of risdiplam patients. 12/25 (48%) of nusinersen patients experienced an SAE, compared to 0 risdiplam patients. 32% of nusinersen patients experienced a treatment-related AE compared to 11% of risdiplam patients.

6.44 The most common AEs in risdiplam patients were teething, viral infection, papule and rhinorrhoea, all of which occurred in 2/7 (29%) of patients. The most common AEs in nusinersen patients were pyrexia (14/15, 93%), upper respiratory tract infection (12/15, 80%) and nasopharyngitis (9/15, 60%).

**Benefits/harms**

6.45 A benefits and harms table was not presented as the resubmission made a claim of non-inferiority in efficacy and safety for both populations 1 and 2.

## **Clinical claim**

### **Population 1 (adult population)**

- 6.46 The resubmission described risdiplam as non-inferior in terms of effectiveness compared with nusinersen and non-inferior in terms of safety compared to nusinersen, with a favourable safety profile in some patients due to differences in administration.
- 6.47 Overall, the ESC considered that the clinical claim of non-inferior efficacy was clinically plausible, consistent with previous comparisons between risdiplam and nusinersen, however, there was a very high level of uncertainty as:
- The quality of evidence was poor and the unanchored naïve comparison carried a substantial risk of bias due to the lack of a common comparator. The clinical claim was based on unanchored naïve side by side numeric comparisons of two risdiplam studies with three nusinersen studies using the outcomes of HFMSE and RULM. Comparisons were made only on point estimates of change from baseline in HFMSE and RULM scores, and statistical comparisons were likely unreliable given the lack of multiplicity adjustments, the use of subgroups and exploratory results.
  - ESC previously considered clinically meaningful benefits in adult patients for HFMSE and RULM (and 6MWT) outcomes were unclear (para 6.22, nusinersen PSD, March 2022 PBAC meeting) and no MCID was nominated for assessment of non-inferiority.
  - The included studies had a high risk of bias due to their trial design, lack of formal statistical testing and heterogeneity. The risdiplam studies also had applicability issues to the proposed PBS population as SUNFISH excluded ambulant patients and JEWELFISH only enrolled patients who had previously been treated with DMTs and enrolled Type 4 SMA patients.
- 6.48 The ESC agreed with the commentary that the claim of non-inferior safety, with a favourable safety profile in some patients, may be reasonable. The PBAC has previously acknowledged that a conclusion of a favourable safety profile of risdiplam over nusinersen in some patients is reasonable given the less invasive route of administration (para 7.8, risdiplam PSD, March 2021 PBAC meeting).
- 6.49 The PBAC considered that the claim of non-inferior comparative effectiveness was reasonable, noting the limitations of the data available.
- 6.50 The PBAC considered that the claim of non-inferior comparative safety was reasonable.

Population 2 (pre-symptomatic 1/2 SMN2 gene copy population)

- 6.51 The resubmission described risdiplam as non-inferior in terms of effectiveness compared with nusinersen and non-inferior in terms of safety compared to nusinersen, with a favourable safety profile in some patients due to differences in administration.
- 6.52 The ESC considered the claim of non-inferior effectiveness was clinically plausible, consistent with previous comparisons between risdiplam and nusinersen. Outcomes for event free survival, HINE-2 total score (at 28/26.1 weeks) and CHOP-INTEND were similar between pre-symptomatic patients with two *SMN2* copies treated with risdiplam (informed by RAINBOWFISH, n=7) and nusinersen (informed by NURTURE, n=15). However, this comparison was associated with a notable degree of uncertainty as:
- The quality of evidence was poor and the unanchored naïve comparison carried a substantial risk of bias due to the lack of a common comparator. The RAINBOWFISH and NURTURE trials both had a high risk of bias given single arm studies with no control group and small patient numbers. Further, RAINBOWFISH data was limited by the short follow-up (median 8.72 months, maximum 16.8 months). Both studies excluded patients aged  $\geq 6$  weeks and no patients with one copy of *SMN2* were enrolled in either trial.
  - Compared to patients treated with risdiplam in RAINBOWFISH, a higher proportion of patients treated with nusinersen in NURTURE were able to stand independently (1/4, 25% compared to 9/15, 60%) and walk independently (1/4, 25% compared to 13/15, 87%). However, this may have been a function of difference in the follow up (12 months for RAINBOWFISH and 34.8 months for NURTURE).
- 6.53 The ESC considered that the claim of non-inferior safety with a favourable safety profile in some patients may be reasonable.
- 6.54 The PBAC considered that the claim of non-inferior comparative effectiveness compared with nusinersen was reasonable, noting the limitations of the data available.
- 6.55 The PBAC considered that the claim of non-inferior comparative safety was reasonable.

***Economic analysis***

- 6.56 For populations 1 and 2, the resubmission presented a cost-minimisation approach (CMA) for risdiplam versus nusinersen. The resubmission sought price parity to nusinersen based on the nusinersen effective price and excluding the cost of nusinersen administration costs.

Population 1 (adult population)

6.57 For the CMA versus nusinersen for population 1, the resubmission considered that over a time horizon of 5 years, risdiplam at 5 mg per day was equi-effective to nusinersen at 12 mg (5 mL) per intrathecal injection administration with 6 administrations in year 1 and 3 administrations from year 2 onwards.

Population 2 (pre-symptomatic 1/2 SMN2 gene copy population)

6.58 For the CMA versus nusinersen for population 2, the resubmission considered that over a time horizon of 5 years, risdiplam at the age and body weight recommended daily dose is equi-effective to nusinersen at 12mg (5 mL) per intrathecal injection administration with 6 administrations in year 1 and 3 administrations from year 2 onwards.

6.59 The calculation of the equi-effective dose required a treatment-initiation age to calculate weight-based dosing for paediatric patients in population 2. The submission's calculation inappropriately assumed patients would begin treatment on the first day of their life, which is unrealistic. Calculation of an effective cost-minimised price for risdiplam for population 2 using a 5-year time horizon starting at the beginning of infancy will result in a notably higher effective price for risdiplam than if the cost-minimisation was conducted for an equi-effective dose once patients had reached a higher weight or at the maximum dose (as for population 1).

Comparison to previous cost-minimisation approach

6.60 In the previous cost minimisation of risdiplam to nusinersen in symptomatic SMA type 1, 2 and 3a in patients  $\leq 18$  years of age, 5 mg of risdiplam daily was considered equi-effective to nusinersen 12 mg (5 mL) every 4 months (i.e. excluding nusinersen loading doses) (para 7.2, risdiplam PSD, March 2021 PBAC meeting). The equi-effective doses proposed in the resubmission were inconsistent with, and less conservative than the previous calculations because:

- Loading doses for nusinersen were included in the calculation for both population 1 and 2. This differed to the CMA in the March 2021 risdiplam PBAC submission where price parity was requested to nusinersen maintenance dosing only (i.e., three administrations per year over five years).
- For population 2 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 both risdiplam and nusinersen.

6.61 PBAC guidelines (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.
- 6.62 At its March 2021 meeting PBAC considered that assuming all patients treated with risdiplam would require 5 mg per day and not including costs for nusinersen loading doses or administration costs was conservative but appropriate, given the limitations of the available evidence for risdiplam and nusinersen and the treatment costs (para 7.9, risdiplam PSD, March 2021 PBAC meeting).
- 6.63 The submission did not justify the differences in approach to the cost-minimisation in symptomatic Type 1-3a patients. Given that it was likely that most patients who are eligible for treatment under the proposed population 2 restriction would otherwise have become eligible for treatment with risdiplam under the current PBS listing (after developing SMA symptoms), the ESC considered the differences in the cost minimisation approach were not justified.
- 6.64 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 the clinical trials (SUNFISH, JEWELFISH and RAINBOWFISH).
- 6.65 ESC noted that if the claims of non-inferior safety and efficacy are accepted by the PBAC, the cost per patient for treatment with risdiplam should be no more than the cost per patient of nusinersen. Where these 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. The ESC considered that it would be appropriate for the calculation of equi-effective doses to be based on the maximum dose of risdiplam (5 mg daily) for both populations, consistent with the equi-effective dose for symptomatic Type 1-3a patients (which would largely comprise the same patients as population 2). The ESC also considered that the equi-effective doses in both populations should be based on steady state dosing, without inclusion of loading doses.
- 6.66 Consistent with the previous risdiplam CMA (para 6.73, risdiplam PSD, March 2021 PBAC meeting), intrathecal administration costs associated with nusinersen administration were included as part of the Population 1 and 2 analyses presented in the resubmission but were not incorporated into the calculation of the risdiplam effective cost-minimised price.
- 6.67 Table 12 presents the results of the CMA using the published prices of risdiplam and nusinersen.

**Table 12: Results of the cost-minimisation approach using published prices <sup>a</sup>**

Component	Risdiplam	Nusinersen
Cost per dose	\$903.49 <sup>b</sup>	\$110,000
Dose duration	Daily	Days 0, 14, 28, and 63. Every 4 months thereafter
Administrations per year	365.25	Year 1: 6 administrations Year 2-5: 3 administrations
Total medicine cost in year 1 <sup>c</sup>	Population 1: \$330,000 Population 2: \$89,369	\$660,000
Total medicine cost per year in years 2-5 <sup>c</sup>	Population 1: \$330,000 Population 2: \$138,011 in year 2 rising to \$282,919 in year 5	\$330,000
Total medicine cost over five years <sup>c</sup>	Population 1: \$1,650,000 Population 2: \$961,169	\$1,980,000
Average yearly cost over five years <sup>c</sup>	Population 1: \$330,000 Population 2: \$192,234	\$396,000
Difference in cost per in year 1	Population 1: Risdiplam = -\$330,000 Population 2: Risdiplam = -\$570,631	
Difference in cost per in years 2-5	Population 1: Risdiplam = \$0 Population 2: Risdiplam = -\$191,989 in year 2 dropping to -\$47,081 in year 5	
Overall difference in cost over five years	Population 1: Risdiplam = -\$330,000 Population 2: Risdiplam = -\$1,018,831	
Difference in average yearly cost over five years	Population 1: Risdiplam = -\$66,000 Population 2: Risdiplam = -\$203,766	

Source: Table 3.6 and 3.7 (p143-4) of the resubmission; 'Cost-minimisation analysis risdiplam 2022' Excel workbook; Calculations during the evaluation based on the preceding data

a – Using the published prices of risdiplam and nusinersen, and assuming population 2 risdiplam patients begin treatment on the first day of their life

b - At the maximum daily dose of 5mg/day (calculated by dividing total risdiplam price over 5 years at a maximum dosage of 5mg /day by the number of days in 5 years)

c – Drug costs only

**Drug cost/patient/year: \$89,369 - \$330,000 (published price)**

6.68 For population 1, based on a dose of 5 mg per day, the maximum dose required, the resubmission estimated a cost of \$330,000 per patient per year, assuming no discontinuations and no wastage, based on the current PBS-listed published price of risdiplam. For population 2, based on the weight-based daily dose of risdiplam and assuming treatment from birth, the resubmission estimated a cost of \$89,369 in year 1, increasing each year up to \$282,919 in year 5, based on the current PBS-listed published price of risdiplam. The published price of risdiplam was used in these calculations as, based on the CMA presented in the submission, the published price of risdiplam resulted in a lower cost per patient than the published price of nusinersen (due to weight-based dosing and nusinersen loading doses).

**Estimated PBS usage & financial implications**

6.69 This resubmission was considered by DUSC.

6.70 The resubmission used an epidemiological approach to estimate the PBS usage of risdiplam in both populations 1 and 2. An SMA incidence of 8.33/100,000 from the NSW/ACT SMA screening program was applied to estimate the total number of SMA patients born each year. This value was lower than used in the March 2021 risdiplam

submission (8.6/100,000) and also in Verhaart (2017) (9.1/100,000), an epidemiological literature review of SMA. As such the incidence of SMA may be underestimated. The financial estimates were sensitive to minor variance in SMA incidence.

**Population 1 (adult population)**

**Table 13: Data sources and parameter values applied in the utilisation and financial estimates for Population 1**

Data	Value	Source	Comment
<b>Eligible population</b>			
Australian live births	Yr 1: 353,462 Yr 2: 358,304 Yr 3: 362,706 Yr 4: 366,687 Yr 5: 370,687 Yr 6: 373,433	ABS 2020 – Live births from 1975-2011  ABS 2012-2030 data	Only patients born from 1975 (aged <48 years) onwards were included. ESC noted that given patients with Type 3 SMA are expected to have a normal life expectancy, this approach underestimates the number of patients with Type 3 SMA in the adult population (Paragraph 6.84, risdiplam PSD, March 2021 PBAC meeting). DUSC considered the eligible population to be significantly underestimated due to the exclusion of patients born prior to 1975. The PSCR acknowledged the number of adult patients could be higher.
Prevalent patients	Yr 1: [REDACTED] 1 Yr 2: [REDACTED] 1 Yr 3: [REDACTED] 1 Yr 4: [REDACTED] 1 Yr 5: [REDACTED] 1 Yr 6: [REDACTED] 1	Combination of literature and ABS data	Likely underestimated, total patient numbers diminish over time due to the use of a prevalence-only approach. DUSC considered this was reasonable but uncertain due to the small number of patients and the differences in life expectancy between Type 2 and 3 SMA patients.
Grandfathered patients	[REDACTED] 1 a	Sponsor subsidised access programs	DUSC noted most grandfather patients would be accounted for in the estimate of prevalent patient numbers.
<b>Treatment utilisation</b>			
Proportion of 'intrathecal ineligible' and 'intrathecal eligible' patients	Intrathecal ineligible = 50%  Intrathecal eligible = 50%	Uptake rate in intrathecal ineligible patients was an assumption. Uptake rate in intrathecal eligible patients was based on responses from the 2022 SMA Adult Advisory Board.  The financial estimates assumed a 100% continuation rate for risdiplam patients.	The assumption that the five Type 1 adult patients were 'intrathecal eligible' and currently receiving nusinersen was reasonable given the likelihood of survival to adulthood without DMT in Type 1 patients was low and these patients were likely on treatment.  DUSC considered the treatment uptake rate for intrathecal eligible patients was underestimated due to the ease of administration of an oral therapy compared to intrathecal therapy.
Uptake rate	Intrathecal ineligible: 100% Intrathecal eligible: Type 1: Yr 1 40% increase by 20% each year Type 2,3: Yr 1 30% increase by 10% each year		
Number treated	Yr 1: [REDACTED] 1 Yr 2: [REDACTED] 1 Yr 3: [REDACTED] 1		

Public Summary Document - March 2023 PBAC Meeting

Data	Value	Source	Comment
	Yr 4: [redacted] <sup>1</sup> Yr 5: [redacted] <sup>1</sup> Yr 6: [redacted] <sup>1</sup>		
Scripts per year	10.5 scripts/ year	Based on 180mg (3 bottles) per script, lasting 36 days at 5mg/day and 365.25 days per year	The WHO weight-by-age data was used to inform weight-based dosing in the financial estimates. However, it was assumed patients initiated treatment at 1 month of age under the justification this aligns with median age at first dose in RAINBOWFISH. This may be reasonable.  Dosage likely underestimated given assumption of no wastage and most optimistic assumption of time of treatment initiation assumption in year 1.
Scripts dispensed	Yr 1: [redacted] <sup>2</sup> Yr 2: [redacted] <sup>2</sup> Yr 3: [redacted] <sup>2</sup> Yr 4: [redacted] <sup>2</sup> Yr 5: [redacted] <sup>2</sup> Yr 6: [redacted] <sup>2</sup>		
Substitution of nusinersen	100% of intrathecal eligible patients	Assumption	No substitution of ONA assumed, which may not be appropriate given clinicians suggest 60.8% of pre-symptomatic patients may use ONA.
Nusinersen scripts offset	3 fewer scripts per patient per year in intrathecal eligible	Consistent with Product Information,	Exclusion of loading doses may underestimate number of doses offset.
Adverse events (AE)	Nil	No cost to management of AEs assumed.	Risdiplam expected to have lower incidence of AEs compared to nusinersen, so omission of AE would increase total financial estimates.
<b>Costs</b>			
Proposed medicine	\$10,841.89	Published price (AEMP) PBS Item 12606L	-
Nusinersen	\$110,000	Published price (AEMP)	-
Patient copayment	\$18.21	PBS utilisation in 2021 for risdiplam	-
MBS costs	\$46.15	Based on clinician advice from the SMA Roundtable meeting 2020. MBS 105, 80% Fee applied in base case. One additional specialist visit for 'intrathecal ineligible' patients per year to reflect that patients would visit a specialist every 6 months on risdiplam versus every 12 months on no treatment.	The resubmission inappropriately double counted patients from previous years as needing additional visits. Given that only prevalent patients were used to estimate population 1 patients, there was no need to consider continuing patients.
Other offsets	\$1,252	DRG B67B, assuming 131% paediatric cost adjustment	Consistent with claims in CMA, but may be overestimated compared to what has previously been accepted for nusinersen administration costs based on MBS items. DUSC commented that MBS cost offsets would likely occur as initiating nusinersen treatment would likely require additional consultations.

a – The financial estimates provided in the resubmission 'exclude grandfather patients' (p162). An option to include the < 500 grandfather patients was included in the Excel workbook, but not turned on when calculating financial estimates.

Source: Table 4.1.1 pp.132-134 of the commentary on the resubmission.

The redacted values correspond to the following ranges:

<sup>1</sup> < 500

<sup>2</sup> 500 to < 5,000

- 6.71 The resubmission stated that only patients born from 1975 onwards were included. As such, patients aged >48 years were not included in the estimates. ESC has previously noted that given patients with Type 3 SMA are expected to have a normal life expectancy, this approach underestimates the number of patients with Type 3 SMA in the adult population (paragraph 6.84, risdiplam PSD, March 2021 PBAC meeting). Including all patients aged over 19 years increased the total cost over the first six years of listing by 76%. The pre-PBAC response acknowledged the uncertainties present when trying to estimate the number of adult SMA patients in Population 1. The pre-PBAC response also noted that the submission's approach (incident cases included from 1975 onwards) to estimating the number of adult patients appeared to estimate a similar patient number as estimated by reports, such as the SMA Australia Values and Perspectives of Adults with SMA report (2020) and insights received from SMA Australia which estimate an adult membership of close to 200 members. The PBAC noted that the submission's estimates assumed a total prevalent adult population of < 500 patients.
- 6.72 The proportion of SMA Types 2 and 3 in population 1 were informed by incidence rates from Verhaart (2017). Six SMA natural history studies were used to inform survival in SMA type 2 patients. These studies were published between 1997-2013, before the current SMA DMT landscape existed, and therefore likely underestimated Type 2 survival. These studies were used to inform the March 2021 risdiplam submission. Normal life expectancy was assumed for Type 3 patients. Five living adult Type 1 SMA patients were added to the estimates. As per Table 2 patients with untreated Type 1 SMA have a life expectancy of 2 years. The submission did not provide treatment details of these patients, however if they received DMTs prior to 18 years of age they would be eligible for treatment under the existing listings and should not be included in population 1.
- 6.73 The resubmission requested listing for < 500 grandfathered patients on a Sponsor-access program. However, the financial estimates provided in the resubmission did not separately account for grandfather patients. PBAC agreed with DUSC that most of these patients would be accounted for in the prevalence estimates.
- 6.74 The submission based several assumptions on data from the 2022 SMA Adult Advisory Board. In the Advisory Board data respondents commented on the reasons some adult patients were not able to be treated with nusinersen, or would prefer an oral treatment, but did not specifically comment on the proportion of patients expected to be eligible/ineligible for intrathecal administration. Some Advisory Board respondents indicated that they expected that up to 90% of their adult SMA patients would be treated with nusinersen. However, the submission assumed that 50% of patients would be ineligible for intrathecal administration.
- 6.75 The resubmission assumed that intrathecal eligible patients will be currently treated with nusinersen based on data from a 2022 SMA Adult Advisory Board. The Advisory Board data was also used to assume uptake rates for risdiplam. The assumption of a risdiplam uptake rate in year 1 of 30% for patients currently treated with nusinersen,

increasing by 10% each year, was applied. The commentary and DUSC considered this may be an underestimate given the benefits of mode of administration and access of risdiplam versus nusinersen. For the intrathecal ineligible patients the submission assumed a 100% uptake rate of risdiplam.

- 6.76 As the majority of additional patients (i.e. patients currently untreated with nusinersen who would be treated with risdiplam) were those assumed to be intrathecal ineligible (see Table 15) this input had a substantial impact on the estimated number of patients treated with risdiplam. Reducing the proportion of intrathecal ineligible patients from 50% to 10% reduced the total risdiplam treated population 1 patients in year 1 from < 500 to < 500.
- 6.77 The resubmission assumed one additional MBS specialist visit per year for patients assumed to switch from no treatment to risdiplam. Reductions in nusinersen administration hospitalisations were included for patients assumed to switch to risdiplam.
- 6.78 Based on PBS script data for August to December 2022, 57 patients received treatment under the nusinersen adult initiation listings (PBS item numbers 13052Y, 13064N, 13068T and 13042N). However, the submission estimated that < 500 adult patients would receive nusinersen in year 1 of the estimates.

Population 2 (pre-symptomatic 1/2 SMN2 gene copy population)

**Table 14: Data sources and parameter values applied in the utilisation and financial estimates in Population 2**

Data	Value	Source	Comments
<b>Eligible population</b>			
Australian live births	Yr 1: 353,462 Yr 2: 358,304 Yr 3: 362,706 Yr 4: 366,687 Yr 5: 370,687 Yr 6: 373,433	ABS 2020 – Live births from 1975-2011  ABS 2012-2030 data	-
Incident patients	Yr 1: [REDACTED] <sup>1</sup> Yr 2: [REDACTED] <sup>1</sup> Yr 3: [REDACTED] <sup>1</sup> Yr 4: [REDACTED] <sup>1</sup> Yr 5: [REDACTED] <sup>1</sup> Yr 6: [REDACTED] <sup>1</sup>	Incident cases based on NSW/ACT experience (n=21/252,081) SMN2 gene copy proportions at birth from this used to extrapolate to likely SMA types	This is slightly underestimated and DUSC considered the number of patients identified pre-symptomatically is likely to increase with application of newborn screening program across Australia.
<b>Treatment utilisation</b>			
Uptake rate	20.8%	Ad board, where: ONA 60.8% risdiplam 20.8% nusinersen 15% nil 2.5%	Unclear whether uptake for risdiplam is reasonable given the safety risks of ONA, and the benefits of administration and access of risdiplam versus nusinersen. It may also have been inappropriate to have assumed the uptake rate remained constant each year as clinicians became more familiar with risdiplam. Utilisation analysis conducted by the DUSC Secretariat noted the current low utilisation of nusinersen and ONA for pre-symptomatic SMA.
Scripts per year	Init: 7.43 Yr 1: 12.11 Yr 2: 9.44	Based on average weight by age in months	Some disparity between timing of start in trial vs weight-by-age assumptions.

Public Summary Document - March 2023 PBAC Meeting

Data	Value	Source	Comments
	Yr 3: 11.0 Yr 4: 12.71 Yr 6: 14.25 Yr 6: 10.15		DUSC considered this assumption to be underestimated particularly in older children due to the wastage associated with liquid formulation.
Scripts dispensed	Yr 1: [redacted] <sup>1</sup> Yr 2: [redacted] <sup>1</sup> Yr 3: [redacted] <sup>1</sup> Yr 4: [redacted] <sup>1</sup> Yr 5: [redacted] <sup>1</sup> Yr 6: [redacted] <sup>1</sup>	Based on average weight by age in months. Number of bottles supplied also differed based on age (Initiation + Yr 1: 1 bottle, Yr 2-Yr 5: 2 bottles, Yr 6 onwards, 3 bottles)	-
Substitution of nusinersen	100%	Assumption	May be overestimated as not all patients would tolerate nusinersen administration
Nusinersen scripts offset	3 fewer scripts per year for all risdiplam patients	Consistent with Product information	Exclusion of loading doses may underestimate number of doses offset
Adverse events (AE)	Nil	No cost to management of AEs assumed.	Risdiplam expected to have lower incidence of AEs compared to nusinersen, so omission of AE would increase total financial estimates.
<b>Costs</b>			
Proposed medicine	\$10,841.89	Published price (AEMP) PBS Item 12606L	-
Nusinersen	\$110,000	Published price (AEMP)	-
Patient copayment	\$18.21	PBS utilisation in 2021 for risdiplam	-
Other offsets	\$1,640	DRG B67B, assuming 131% paediatric cost adjustment	Consistent with claims in CMA, but may be overestimated compared to what has previously been accepted for nusinersen administration costs based on MBS items

Source: Table 4.1.1 pp.132-134 of the commentary on the resubmission.

The redacted values correspond to the following ranges:

<sup>1</sup> < 500

- 6.79 The resubmission assumed only incident (newborn) patients would make up the population 2 patient numbers. This may not have been appropriate as it excludes currently living patients aged <36 months in Year 1. PBS script data for 2022 indicates there were ≤5 patients who received initial treatment under the pre-symptomatic listings for nusinersen (PBS items 12176W and 12177X), and ≤5 patients who received treatment with ONA. The number of patients identified pre-symptomatically is likely to increase with wider application of newborn screening.
- 6.80 The proportion of patients with two *SMN2* gene copy numbers (57.1%) was sourced from the NSW/ACT SMA screening program and applied to estimate the total incident population. The resubmission reasonably assumed no patients with one copy of the *SMN2* gene would be included in population 2 as these patients would likely be symptomatic at birth.
- 6.81 The resubmission used age and weight-based dosing data, as was used to inform the CMA, in the financial estimates for population 2. However, the risdiplam doses

assumed in the CMA were lower than in the financial estimates due to weight changes being estimated monthly rather than annually. Additionally, dosages of risdiplam in population 2 during the first 6 years of listing (in which patients weigh less than 20 kg for the first 5 years) would be substantially lower than the dosages of risdiplam after year 6 (in which they would be using the maximum dose of 5 mg/daily), and as such, the financial estimates of the first 6 years of listing in population 2 do not reflect the total cost of listing of risdiplam beyond 6 years.

- 6.82 Uptake rates (20.8%) were sourced from advisory board responses. It is unclear whether an assumption of 20.8% uptake for risdiplam is reasonable given the safety risks of alternative DMTs such as ONA, and the benefits of administration and access of risdiplam versus nusinersen. It may also have been inappropriate to have assumed the uptake rate of 20.8% remained constant over each year as clinicians become more familiar with risdiplam.
- 6.83 Reductions in nusinersen administration (based on AR DRG hospitalisations costs) were included for patients assumed to switch to risdiplam. The unit cost for administration in the resubmission (\$1,252 in adults and \$1,640 in children) was substantially higher than administration costs applied in the nusinersen July 2020 submission (\$402.25, Table 18, nusinersen, PSD, July 2020 PBAC meeting).

Estimation of use and financial impact

- 6.84 The resubmission used published risdiplam and nusinersen prices to estimate financial impacts.

Table 15 Financial estimates in population 1 and 2 using published prices

	2023	2024	2025	2026	2027	2028
<b>Population 1 patient estimates</b>						
Total prevalent patients	█ 1	█ 1	█ 1	█ 1	█ 1	█ 1
Treated with ris:						
Intrathecal eligible	█ 1	█ 1	█ 1	█ 1	█ 1	█ 1
Intrathecal ineligible	█ 1	█ 1	█ 1	█ 1	█ 1	█ 1
Total population 1 patients treated (ris)	█ 1	█ 1	█ 1	█ 1	█ 1	█ 1
<b>Population 2 patient estimates</b>						
Population 2 patients treated (ris)	█ 1	█ 1	█ 1	█ 1	█ 1	█ 1
<b>Scripts</b>						
Number of ris scripts population 1 <sup>a</sup>	█ 2	█ 2	█ 2	█ 2	█ 2	█ 2
Number of ris scripts population 2 <sup>b</sup>	█ 1	█ 1	█ 1	█ 1	█ 1	█ 1
<b>Cost</b>						
Net cost population 1	█ 3	█ 3	█ 3	█ 8	█ 8	█ 8
Net cost population 2	█ 4	█ 4	█ 4	█ 4	█ 4	█ 4
Net cost population 1+2	█ 3	█ 3	█ 8	█ 8	█ 8	█ 9
Net offset from nusinersen	█ 5	█ 5	█ 5	█ 6	█ 6	█ 6
Net cost to PBS/RPBS population 1+2	█ 6	█ 6	█ 6	█ 6	█ 6	█ 6
MBS cost (population 1)	█ 4	█ 4	█ 4	█ 4	█ 4	█ 4
Hospital cost offset (population 1+2)	█ 7	█ 7	█ 7	█ 7	█ 7	█ 7
<b>Total cost to government population 1+2</b>	█ 6	█ 6	█ 6	█ 6	█ 6	█ 6

Source: Table 4.9, p160, table 4.10, table 4.21, p170, table 4.22, p170, table 4.38, p178 of the resubmission Section 4 Workbook Risdiplam 2022.xlsx

a - Assumed each patient will use 10.15 scripts, with 3 bottles per script, per year

b - Based on patient weight which was informed by WHO 50<sup>th</sup> percentile (see Table 4.1.1 of the commentary)

The redacted values correspond to the following ranges:

<sup>1</sup> < 500

<sup>2</sup> 500 to < 5,000

<sup>3</sup> \$30 million to < \$40 million

<sup>4</sup> \$0 to < \$10 million

<sup>5</sup> \$10 million to < \$20 million

<sup>6</sup> \$20 million to < \$30 million

<sup>7</sup> net cost saving

<sup>8</sup> \$40 million to < \$50 million

<sup>9</sup> \$50 million to < \$60 million

6.85 The resubmission estimated a total cost of \$20 million to < \$30 million in year 1 decreasing to \$20 million to < \$30 million in year 6 using the published price for risdiplam.

6.86 Overall DUSC considered the number of eligible patients and patients treated in population 1 presented in the submission to be significantly underestimated. In addition to excluding patients older than 48 years and potentially underestimated treatment uptake from patients currently treated with nusinersen, DUSC noted that

scripts per year for both populations were underestimated due to wastage associated with liquid formulations.

### **Financial Management – Risk Sharing Arrangements**

- 6.87 For population 1, the resubmission proposed an increase in the Risk Sharing Agreement (RSA) subsidisation cap currently in place for nusinersen in order to account for the additional population 1 patients who would be eligible to access PBS-subsidised risdiplam therapy who were otherwise not receiving therapy. The pre-PBAC response further stated that ‘a reasonable and justifiable approach to the expansion of the expenditure caps would be an increase, commensurate with the incremental cost of Population 1.’
- 6.88 For population 2, the resubmission stated the Sponsor is willing to enter into the existing nusinersen RSA.

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

## **7 PBAC Outcome**

- 7.1 The PBAC recommended the listing of risdiplam for adults diagnosed with 5q spinal muscular atrophy (SMA) with symptom onset prior to 19 years of age and no initiation of disease-modifying treatment (DMT) during childhood (population 1) and patients aged <36 months with a confirmed genetic diagnosis of SMA (*SMA1* deletion or mutation) who have an *SMN2* gene copy number of 1 or 2 and are pre-symptomatic (population 2) on the basis that it should be available only under special arrangements under Section 100. The PBAC’s recommendation for listing in these populations 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. The PBAC noted that the sponsor withdrew the request for listing of risdiplam for patients aged <36 months with a confirmed genetic diagnosis of SMA (*SMA1* deletion or mutation) who have a *SMN2* gene copy number of 3 and are pre-symptomatic.
- 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 in patients with SMA type 1-3 (paragraph 7.2, risdiplam PSD, March 2021 PBAC meeting).
- 7.3 The PBAC acknowledged that there is a clinical need for an orally administered treatment for SMA, noting the important factors for patients and carers associated with the less invasive route of administration. As identified in consumer comments, risdiplam has advantages in reducing the treatment burden for patients in terms of increasing independence and reducing the need for patients to travel to specialist hospitals for administration of treatment. The PBAC also noted that there are likely to be patients for whom intrathecal administration of nusinersen is not feasible due to high grade scoliosis.

- 7.4 The PBAC considered that it was reasonable for the restrictions for populations 1 and 2 to align with the existing restrictions for nusinersen, with the exception of criteria relating to loading doses, which are not relevant to risdiplam. The PBAC considered that for population 1 it was appropriate to include criteria in the initial treatment listing to allow treatment of patients who had previously accessed risdiplam via non-PBS supply (e.g. clinical trial or sponsor compassionate access), who would otherwise have met the PBS criteria. The PBAC noted that this would negate the need for a separate grandfather listing. The PBAC recalled it previously considered the restrictions for nusinersen (in adult patients) should require that assessment of suitability for continuation of treatment takes place every 6 months after 2 years of treatment (para 3.7, nusinersen PSD, March 2022 PBAC meeting). The PBAC considered that the number of repeats in the initial and continuing listings for risdiplam should align with this recommendation for assessment of suitability for continuation of treatment.
- 7.5 For populations 1 and 2, the resubmission appropriately nominated nusinersen as the main comparator. For population 2 the PBAC also considered that ONA is a relevant comparator for patients aged <9 months of age.
- 7.6 The PBAC noted that the clinical evidence presented consisted of unanchored naïve side by side comparisons of point estimates for several outcomes. No formal comparison was made on any of the outcomes provided, and no MCID was proposed to allow assessment of non-inferiority. The PBAC noted that the evidence in population 1 was based on single-arm nonrandomised studies with a high risk of bias and limited applicability to the proposed PBS population. In addition there was significant heterogeneity between the studies and follow up was limited. In population 2 the studies had very small sample sizes (n=18-25), and short follow up of outcomes as well as differences in assessment times for specific outcomes. In addition, no comparison to ONA was presented. Overall, the PBAC considered that the evidence provided was of poor quality, particularly for population 1. However, the PBAC considered that for both populations the clinical claim of non-inferior efficacy was clinically plausible, consistent with previous comparisons between risdiplam and nusinersen, noting the limitations of the data available.
- 7.7 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).
- 7.8 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 also noted that for population 2 the proposed equi-effective doses were based on weight-based dosing for paediatric patients assuming that patients begin treatment at birth. This underestimated the use of

risdiplam as doses are higher in older infants and children and hence increased the cost-minimised price for risdiplam. In addition, the PBAC noted 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.

- 7.9 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.
- 7.10 Overall, the Commentary and DUSC considered the number of eligible patients and patients treated in population 1 was likely underestimated due to not accounting for patients older than 48 years and potentially underestimating the substitution from nusinersen. However, the PBAC noted the actual use of nusinersen in adult patients was substantially less than estimated (57 as at December 2022 based on PBS data vs < 500 estimated for year 1). The PBAC noted that early uptake of nusinersen in the adult population appears to be below expected levels despite a high level of awareness and anticipation for the August 2022 listing for the adult population. In addition, the proportion of patients considered ineligible for intrathecal administration was uncertain and likely lower than estimated in the submission, and the financial estimates were sensitive to the estimate of the SMA prevalence. The PBAC also considered that Type 1 SMA patients should be removed from the estimates as these patients are unlikely to have reached adulthood without treatment. Overall, the PBAC considered that the patient numbers for risdiplam in population 1 are highly uncertain.
- 7.11 For population 1, the resubmission proposed an increase in the Risk Sharing Arrangement (RSA) subsidisation caps currently in place for nusinersen to account for additional patients who would access PBS-subsidised risdiplam therapy but otherwise would not receive therapy. The PBAC considered that given the lower than expected early uptake of nusinersen in the adult population, and uncertainty regarding risdiplam patient estimates, no increase to the caps was justified at this time. The PBAC considered a more reliable estimate of risdiplam use, and in particular the proportion ineligible for intrathecal administration, together with estimates that better reflect the actual use of nusinersen, would be required for revisions to the financial caps.
- 7.12 For population 2, the resubmission stated the sponsor is willing to enter into the existing nusinersen RSA. The PBAC considered that this approach would be reasonable

as the listing of risdiplam is unlikely to result in increased utilisation in this patient population.

- 7.13 The PBAC recalled that it had recommended PBS listing of nusinersen in the Type 3b population at the July 2021 PBAC meeting, and had advised that this extension to include paediatric patients with symptom-onset between 3 and 18 years [i.e., Type 3b] could also be flowed onto risdiplam using the equi-effective doses established for Type 1, 2 and 3a [from the risdiplam versus nusinersen cost-minimisation used to inform the risdiplam recommended listing] (para 7.23, nusinersen PSD, July 2021 PBAC meeting). At the time of PBAC consideration the sponsor had not progressed this extension to the risdiplam listing to include Type 3b patients. The PBAC considered that a pricing offer for the 3b population would be welcomed, in order to ensure that there is equity of access to risdiplam across all type 1-3 SMA patients.
- 7.14 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because risdiplam is not expected to address a high and urgent unmet clinical need given the presence of alternative therapies, the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were not met.
- 7.15 The PBAC noted that this submission is not eligible for an Independent Review as it is a positive recommendation.

**Outcome:**

Recommended

## 8 Recommended listing

### 8.1 Amend existing item:

#### Population 1 – adult initiation

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No.of Rpts	Available brands
RISDIPLAM					
risdiplam 750 microgram/mL powder for oral liquid, 80 mL	NEW	3	3	7	Evrysdi
<b>Restriction Summary</b>					
Concept ID (for internal Dept. use)	Category / Program: Section 100 – Highly Specialised Drugs Program				
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners				
	Restriction type: <input checked="" type="checkbox"/> Authority Required (in writing only via post/HPOS upload)				
	Administrative Advice: No increase in the maximum quantity or number of units may be authorised.				
	Administrative Advice: No increase in the maximum number of repeats may be authorised.				
	Administrative Advice: Special Pricing Arrangements apply.				

Public Summary Document - March 2023 PBAC Meeting

	<b>Indication:</b> Spinal Muscular Atrophy (SMA)
	<b>Treatment Phase:</b> Initial PBS-subsidised treatment in an adult who did not initiate PBS subsidy during childhood
	Must be treated by a specialist medical practitioner experienced in the diagnosis/management of SMA; or
	Must be treated by a medical practitioner who has been directed to prescribe this benefit by a specialist medical practitioner experienced in the diagnosis/management of SMA
	AND
	Patient must be undergoing initial PBS-subsidised treatment 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).
	AND
	Patient must be undergoing concomitant treatment with best supportive care, but this benefit is the sole PBS-subsidised disease modifying treatment
	<b>Clinical criteria</b>
	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
	<b>Clinical criteria</b>
	Patient must not be receiving invasive permanent assisted ventilation in the absence of a potentially reversible cause while being treated with this drug
	<b>Population criteria</b>
	Patient must be at least 19 years of age at the time of this authority application, but never claimed PBS subsidy for a disease modifying treatment during childhood
	AND
	Patient must have SMA where the onset of signs/symptoms (at least one) of SMA first occurred prior to their 19th birthday (SMA symptom onset after this age will be considered type IV SMA, which is not PBS-subsidised)
	<b>Prescribing Instructions:</b>
	Invasive permanent assisted ventilation means ventilation via tracheostomy tube for greater than or equal to 16 hours per day.
	Signs and symptoms of spinal muscular atrophy in the context of this PBS restriction are: (i) Failure to meet or regression in ability to perform age-appropriate motor milestones (ii) Proximal weakness (iii) Hypotonia (iv) Absence of deep tendon reflexes (v) Failure to gain weight appropriate for age (vi) Any active denervation or chronic neurogenic changes found on electromyography (vii) A compound muscle action potential below normative values for an age-matched child
	In this authority application, confirm: (1) the patient's medical history is consistent with a diagnosis of childhood onset spinal muscular atrophy, (2) which of the above (i to vii) (at least 1) were present during childhood, (3) the age of the patient (rounded to the nearest year) when the first sign/symptom was observed.
	<b>Administrative Advice</b>
	An outcome on the authority application is not immediate, but will follow in due course. Electronic upload is encouraged to reduce processing time.

Public Summary Document - March 2023 PBAC Meeting

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 <a href="http://www.servicesaustralia.gov.au">www.servicesaustralia.gov.au</a> , Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at <a href="http://www.servicesaustralia.gov.au/hpos">www.servicesaustralia.gov.au/hpos</a> , Or mailed to:., Services Australia, Complex Drugs, Reply Paid 9826, HOBART TAS 7001								
<b>MEDICINAL PRODUCT</b> medicinal product pack				<b>PBS</b> <b>item</b> <b>code</b>	<b>Max.</b> <b>qty</b> <b>packs</b>	<b>Max.</b> <b>qty</b> <b>units</b>	<b>No.of</b> <b>Rpts</b>	<b>Available brands</b>
RISDIPLAM								
risdiplam 750 microgram/mL powder for oral liquid, 80 mL				NEW	3	3	5	Evrysdi
<b>Restriction Summary</b>								
<b>Concept ID</b> (for internal Dept. use)		<b>Category / Program:</b> Section 100 – Highly Specialised Drugs Program						
		<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners						
		<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required (electronic)						
Prescribing rule level		<b>Administrative Advice:</b> No increase in the maximum quantity or number of units may be authorised.						
		<b>Administrative Advice:</b> No increase in the maximum number of repeats may be authorised.						
		<b>Administrative Advice:</b> <i>Special Pricing Arrangements apply.</i>						
		<b>Indication:</b> Spinal Muscular Atrophy (SMA)						
		<b>Treatment Phase:</b> Continuing/maintenance treatment in an adult where treatment was initiated in adulthood						
		<b>Treatment criteria:</b>						
		Must be treated by a specialist medical practitioner experienced in the diagnosis/management of SMA; or						
		Must be treated by a medical practitioner who has been directed to prescribe this benefit by a specialist medical practitioner experienced in the diagnosis/management of SMA						
		<b>AND</b>						
		Patient must be undergoing continuing PBS-subsidised treatment that was initiated through the Initial treatment listing for SMA initiated in adulthood						
		<b>AND</b>						
		Patient must be undergoing concomitant treatment with best supportive care, but this benefit is the sole PBS-subsidised disease modifying treatment						
		<b>AND</b>						
		<b>Clinical criteria:</b>						
		The treatment must be each of: (i) occurring from week 104 onwards relative to the first administered dose, (ii) demonstrating a clinically meaningful response; or						
		The treatment must be occurring within the first 104 weeks from the first administered dose						
		<b>AND</b>						
		<b>Clinical Criteria</b>						
		Patient must not be receiving invasive permanent assisted ventilation in the absence of a potentially reversible cause while being treated with this drug						
		<b>Prescribing Instructions</b>						

Public Summary Document - March 2023 PBAC Meeting

	Invasive permanent assisted ventilation means ventilation via tracheostomy tube for greater than or equal to 16 hours per day.
	<p>Where this authority application seeks to continue treatment beyond the first 104 weeks of treatment, comprehensive assessment must be undertaken periodically and documented, involving the patient and the treating physician to establish agreement that treatment is continuing to produce a clinically meaningful response.</p> <p>A clinically meaningful response is present where an improvement, stabilisation or minimal decline in symptoms has occurred as a result of this drug treatment and where there is agreement between the treating physician and patient over what constitutes improvement, stabilisation, or minimal decline.</p> <p>PBS subsidy must cease if there is no agreement on whether a clinically meaningful response is present. Undertake re-assessments for a clinically meaningful response at least every six months. Document these re-assessments in the patient's medical records.</p> <p>In undertaking comprehensive assessments, where practical, a clinically meaningful response assessment encompasses the patient's motor function as assessed using an instrument like the Revised Upper Limb Module (RULM), Hammersmith Functional Motor Scale - Expanded (HFMS) or 6-minute walk test (6MWT), and the patient's quality of life including, but not limited to, level of independence. Quality of life may be informed by use of the SMA Health Index (SMA-HI) or SMA Functional Rating Scale (SMAFRS).</p>
	<b>Administrative Advice</b>
	<p>Literature references for various instruments measuring motor function and quality of life in the context of spinal muscular atrophy are: Revised Upper Limb Module, Mazzone et al. 2017. Revised upper limb module for spinal muscular atrophy: Development of a new module. Muscle &amp; Nerve 55(6):869-874, Hammersmith Functional Motor Scale - Expanded, Ramsey et al. 2017. Revised Hammersmith Scale for spinal muscular atrophy: A SMA specific clinical outcome assessment tool. PLoS ONE 12(2): e0172346. doi:10.1371/journal.pone.0172346., 6-Minute Walk Test (6MWT), American Thoracic Society. 2002. ATS statement: Guidelines for the six-minute walk test. American Journal of Respiratory and Critical Care Medicine 166(1), pp 111-117, The National Heart Foundation of Australia has 6MWT test standardised instructions and recording forms located at: <a href="https://www.heartonline.org.au/resources/documents-and-links#exercise">https://www.heartonline.org.au/resources/documents-and-links#exercise</a>, SMA Health Index, Zizzi et al. 2021. The Spinal Muscular Atrophy Health Index (SMA-HI): A Novel Outcome for Measuring How a Patient Feels and Functions. Muscle &amp; Nerve 63(10), pp 837-844, SMA Functional Rating Scale, Elsheikh et al. 2018. Reliability of Spinal Muscular Atrophy Functional Rating Scale (SMAFRS) in Ambulatory Adults with Spinal Muscular Atrophy. Neurology April (15 Supplement) P4.452</p>
	Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see <a href="http://www.servicesaustralia.gov.au/HPOS">www.servicesaustralia.gov.au/HPOS</a> ) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).

Population 2/3 – paediatric, pre-symptomatic

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
RISDIPLAM					
risdiplam 750 microgram/mL powder for oral liquid, 80 mL	NEW	1	1	0	Evrysdi
<b>Restriction Summary</b>					
Concept ID (for internal Dept. use)	<b>Category / Program:</b> Section 100 – Highly Specialised Drugs Program				
	<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners				
	<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required (in writing only via post/HPOS upload)				

Public Summary Document - March 2023 PBAC Meeting

Prescribing rule level	<b>Administrative Advice:</b> No increase in the maximum quantity or number of units may be authorised.
	<b>Administrative Advice:</b> No increase in the maximum number of repeats may be authorised.
	<b>Administrative Advice:</b> Special Pricing Arrangements apply.
	<b>Administrative Advice:</b> 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 <a href="http://www.servicesaustralia.gov.au">www.servicesaustralia.gov.au</a> , Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at <a href="http://www.servicesaustralia.gov.au/hpos">www.servicesaustralia.gov.au/hpos</a> , Or mailed to: Services Australia, Complex Drugs, Reply Paid 9826, HOBART TAS 7001
	<b>Administrative Advice:</b> Recognised hospitals in the management of SMA are Queensland Children's Hospital (Brisbane), Royal Children's Hospital Melbourne, Monash Children's Hospital (Melbourne), John Hunter Hospital (Newcastle), Sydney Children's Hospital Randwick, Children's Hospital at Westmead, Adelaide Women and Children's Hospital and Perth Children's Hospital.
	<b>Indication:</b> Pre-symptomatic Spinal Muscular Atrophy (SMA)
	<b>Treatment Phase:</b> Initial treatment of pre-symptomatic spinal muscular atrophy (SMA)
	<b>Treatment criteria:</b>
	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
	<b>Clinical criteria:</b>
	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
	<b>AND</b>
	<b>Clinical Criteria:</b>
	The condition must have genetic confirmation that there are 1 to 2 copies of the survival motor neuron 2 (SMN2) gene
	<b>AND</b>
	<b>Clinical Criteria:</b>
	The condition must be pre-symptomatic
	<b>AND</b>
	<b>Clinical Criteria:</b>
	The treatment must be given concomitantly with best supportive care for this condition
	<b>AND</b>
	<b>Clinical Criteria:</b>
	Patient must be untreated with gene therapy
	<b>Population criteria:</b>
	Patient must be aged under 36 months prior to commencing treatment
	<b>Prescriber instructions</b>

Public Summary Document - March 2023 PBAC Meeting

	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 <i>SMN2</i> gene copies determined by quantitative polymerase chain reaction (qPCR) or multiple ligation dependent probe amplification (MLPA)					
	<b>Administrative advice</b>					
	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	No. of Rpts	Available brands
RISDIPLAM						
risdiplam 750 microgram/mL powder for oral liquid, 80 mL		NEW	1	1	5	Evrysdi
<b>Treatment of Concept 12606L</b>						
Concept ID (for internal Dept. use)	<b>Category / Program:</b> Section 100 – Highly Specialised Drugs Program					
	<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners					
	<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required (electronic)					
Prescribing rule level	<b>Administrative Advice:</b> No increase in the maximum quantity or number of units may be authorised.					
	<b>Administrative Advice:</b> No increase in the maximum number of repeats may be authorised.					
	<b>Administrative Advice:</b> Special Pricing Arrangements apply.					
	<b>Administrative Advice:</b> Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see <a href="http://www.servicesaustralia.gov.au/HPOS">www.servicesaustralia.gov.au/HPOS</a> ) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).					
<b>Indication:</b> Spinal Muscular Atrophy (SMA)						
<b>Treatment Phase:</b> Continuing/maintenance treatment of either symptomatic Type I, II or IIIa SMA, or of a patient commenced on this drug under the pre-symptomatic SMA listing						
<b>Treatment criteria:</b>						
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; or initiated 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						
<b>AND</b>						
<b>Treatment criteria:</b>						
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						
<b>Clinical criteria:</b>						
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						
<b>AND</b>						
<b>Clinical criteria:</b>						

	The treatment must not be in combination with PBS-subsidised treatment with nusinersen for this condition
	<b>AND</b>
	<b>Clinical criteria:</b>
	The treatment must be given concomitantly with best supportive care for this condition
	<b>AND</b>
	<b>Clinical criteria:</b>
	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
	<b>Population criteria:</b>
	Patient must have been 18 years of age or younger at the time of initial treatment with this drug
	<b>Prescriber instructions:</b>
	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.

***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

Roche welcomes the PBAC's decision to recommend risdiplam for two populations.

As proposed by Roche and acknowledged by the PBAC, the availability of an orally administered treatment for SMA on the PBS will mean more patients will be able to access treatment for their SMA.

Roche requested an adjustment to the RSA arrangements currently in place for nusinersen to account for additional patients who would access PBS-subsidised risdiplam therapy but otherwise would not receive therapy due to the administration route of the current standard of care. Roche looks forward to working with the PBAC in the future to revise these arrangements.

In the interim, Roche is working with the Department of Health towards a PBS listing in both patient population groups at the earliest opportunity.