Changes have been made to this item. Details of the corrigendum are at the end of this document.

5.15 RISDIPLAM, Powder for oral solution 0.75 mg per 1mL, 80 mL, Evrysdi®, Roche Products Pty Ltd.

1 Purpose of Application

1.1 The submission requested a Section 100, Highly Specialised Drugs Program, Authority Required listing for risdiplam for treatment of spinal muscular atrophy (SMA) for the following patient populations.

- Population 1 – SMA Types 1, 2 and 3a in patients aged 18 years or under (i.e. <19 years) at treatment initiation;
- Population 2 – SMA Type 3b in patients aged 18 years or under at treatment initiation; and
- Population 3 – SMA Types 1, 2 or 3 in patients aged over 18 years (i.e. 19 years and above) at treatment initiation.

1.2 The requested basis for listing was:

- Population 1 – a cost-minimisation analysis versus nusinersen;
- Population 2 – the submission provided no analysis to support listing for patients in population 2, with SMA Type 3b patients not explicitly modelled; and
- Population 3 – a cost-utility analysis versus best supportive care (BSC).

1.3 The submission considered that the cost-effectiveness for population 2 would be informed by the analyses presented for populations 1 and 3, which the ESC considered was not reasonable, given patients in populations 2 and 3 were different in both age and likely disease progression. The Pre-Sub-Committee Response (PSCR) stated that the sponsor and its clinical advisors deem Population 2 sufficiently comparable to patients diagnosed with Type 3a SMA but in the absence of clinical evidence specifically for this subgroup of patients alone, proposed to [redacted] the budgetary impact of treating these patients within the Risk Share Arrangement (RSA) [redacted].

Table 1: Key components of the clinical issue addressed by the submission

Component	Description		
	Population 1	**Population 2**	**Population 3**
Populations	18 years of age and under SMA Type 1, 2 and 3a.	18 years of age and under with SMA Type 3b.	Over 18 years of age with SMA Ty pe 1, 2 or 3.
Intervention	Risdiplam orally administered powder for solution given daily. Dose is age/weight dependent (0.20 mg/kg for >2month and <2 years of age, 0.25 mg/kg for ≥2 years of age and <20kg, and 5mg for ≥2 years of age and ≥20kg).		
Comparators	Nusinersen 12mg intrathecally administered solution for injection every 4 months.	Best supportive care.	Best supportive care.
Outcomes	Type 1 SMA: Sitting without support for at least 5 seconds (BSID-III), event free survival (EFS), overall survival (OS), motor milestones as measured by the CHOP-INTEND and HINE-2 Type 2 and 3 SMA: MFM32, RULM, HFMSE, SMAIS		
Clinical claims	In patients 18 years of age and under with Type 1, 2 or 3a SMA, risdiplam is non-inferior in terms of efficacy compared with nusinersen; risdiplam is non-inferior in terms of safety compared with nusinersen, with a favourable safety profile in some patients due to differences in administration (oral vs intrathecal).	In patients 18 years of age and under with Type 3b SMA, risdiplam is superior to standard of care in terms of efficacy; risdiplam is inferior in terms of safety, with minimal treatment-related adverse events that are clinically manageable.	In patients over 18 years of age with SMA Type 1, 2 or 3, risdiplam is superior to standard of care in terms of efficacy; risdiplam is inferior in terms of safety, with minimal treatment-related adverse events that are clinically manageable.

BSID-III=Bayleys Scales of Infant and Toddler Development Third Edition; 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, SMAIS=spinal muscular atrophy independent scale
Note: While Population 3 does include Type 1 SMA adult patients, the submission expected that this would comprise of a very small number of patients, with only approximately 5 known Type 1 SMA adult patients in Australia. Therefore, the submission considered Population 3 to be a predominately 'Type 2 and 3' adult SMA population.
Source: Table 1.1, p4 of the submission.

2 Background

Registration status

2.1 The submission was made under TGA/PBAC Parallel Process, with TGA approval anticipated by April 2021. The delegate's overview was available 3 March 2021. The delegate sought ACM advice regarding:

- the process for diagnosing 5q SMA in Australia;
- the proposed indication, specifically inclusion of patients <2 months of age, patients with Type 0 and Type IV SMA and pre-symptomatic patients;
- limiting prescribing to medical specialists with experience in the diagnosis and management of SMA; and
- toxicity concerns.

2.2 The proposed TGA indication is:

"… for the treatment of 5q spinal muscular atrophy (SMA)".

3 Requested listing

3.1 A summary of the requested restrictions is provided in the table below.

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Price for Max. Qty*	Proprietary Name and Manufacturer	
Populations 1 and 2					
RISDIPLAM Powder for oral solution 60mg	1	5	$13,058.01 private published price $[redacted] private effective price $13,010.27 public published price $[redacted] public effective price	EVRYSDI®	Roche
Population 3					
RISDIPLAM Powder for oral solution 60mg	3	5	$39,078.54 private published price $[redacted] private effective price $39,030.80 public published price $[redacted] public effective price	EVRYSDI®	Roche

Condition:	Spinal muscular atrophy
PBS Indication:	Treatment of spinal muscular atrophy
Restriction: Section 100 (Highly specialised drugs program)	☒Authority Required - In Writing (for initial therapy) ☒Authority Required – Telephone (for continuing therapy)
Treatment criteria:	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.
For initial therapy	The condition must have 5q homozygous deletion, mutation of, or compound heterozygous mutation in the SMN1 gene of type I, II or III, AND Patient must have experienced at least two of the defined signs and symptoms of SMA type I, II or III, AND The treatment must be given concomitantly with best supportive care for this condition, AND The treatment must not be in combination with other disease modifying treatments for this condition, AND The treatment must not be initiated within 120 days of previous treatment with nusinersen, AND Patients must be 18 years of age or under (population 1 and 2) or must be over 18 years of age (population 3)
For continuing therapy	Patient must have previously received PBS-subsidised treatment with this drug for this condition, AND The treatment must not be in combination with other disease modifying treatments for this condition, AND 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, AND The treatment must be given concomitantly with best supportive care for the condition; AND In patients who initiated treatment when they were over 18 years of age (population 3), patient must have demonstrated maintenance or improvement of motor function

*Note the effective prices as based on price parity to nusinersen and detailed in the cost-minimisation analysis in Section 3B are presented in Table 5 in the CIC section of the Executive Summary.
Source: Table 1.8 and 1.9, p26 of the submission.

3.2 The submission requested a Special Pricing Arrangement (SPA), with the published price and effective price of risdiplam calculated on a cost-minimisation basis with nusinersen.

3.3 The requested listing requires the condition to be '5q homozygous deletion, mutation of, compound heterozygous mutation in the SMN1 gene of type I, II or III', however it was unclear whether the results of these tests would be available for older patients initiating treatment. The cost of a test for deletion or mutation in the SMN1 gene is not funded by the MBS and patients will generally rely on public hospital systems to cover the costs of such testing. The cost of SMN1 testing was not included in the economic evaluation or financial estimates.

3.4 The PBAC noted that the restriction would need to be revised to reflect the population for whom PBS listing was recommended. There may be potential for use outside the requested restriction in adult patients and patients with Type 3b or Type 4 SMA. There is also the potential for use outside the restriction in pre-symptomatic patients identified with SMA through newborn screening programs.

3.5 The PBAC noted that the proposed restriction does not allow concomitant use of risdiplam with other disease modifying treatments for SMA, but no restrictions on previous treatments were proposed. The PBAC considered that it would be appropriate for patients previously treated with nusinersen to receive risdiplam. The PBAC foreshadowed that if additional disease modifying treatments for SMA are listed on the PBS further consideration may need to be given to restrictions regarding their use prior to risdiplam.

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

4 Population and disease

4.1 SMA is a rare autosomal recessive progressive neuromuscular disease caused by mutations or deletions in the Survival-of-Motor-Neuron 1 (SMN1) gene on chromosome 5q. Alterations to this gene result in deficiency of SMN protein, which in turn results in loss of motor function, muscle weakness and complications such as respiratory issues, contractures and scoliosis. Patients with SMA typically develop weak muscles and may have trouble walking and breathing. SMA is classified into types (0, 1, 2, 3 and 4) and subtypes (a, b, and sometimes by subgroup c) based on age of onset and maximal motor function achieved.

4.2 There is a clinical spectrum of disease with earlier age of onset being associated with lower numbers of SMN2 gene copies and increased severity of symptoms. Table 2 outlines the relationship between SMA type and SMN2 copy number as well as the life expectancy, typical symptoms and expected motor function for each SMA type.

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 SMN2 copy number^	Population included in proposed PBS listing
0	Prenatal	X	X	X	Severe hypotonia*	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*	>3 years	✓	✓	Assisted	Later loss of ambulation			✓
4	>18 years	✓	✓	✓	Slow, progressive muscle weakness. Ambulant until later in life.	Normal	4, 5, 6	X

*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.
Source: Table 1.2, p6 of the submission.

4.3 Risdiplam is an orally administered treatment that corrects the splicing of SMN2 to shift the balance from exon 7 exclusion to exon 7 inclusion into the mRNA transcript, leading to a sustained increase in the expression of functional SMN protein from the SMN2 gene. It has a similar mechanism of action to nusinersen, however risdiplam crosses the blood-brain barrier, and thereby results in an increase in SMN protein in both the central nervous system (CNS) and the periphery, whereas nusinersen results in an increase in SMN protein in the CNS only.

5 Comparator

5.1 For population 1: The submission appropriately nominated nusinersen delivered via intrathecal injections as the comparator. Nusinersen is the only publicly funded disease modifying treatment for SMA in Australia and is currently PBS listed for symptomatic SMA Types 1, 2, and 3a in patients up to and including 18 years of age, with onset of symptoms prior to 3 years of age. For any patients ineligible, or considered unsuitable for nusinersen, BSC, consisting of therapies directed at providing nutrition and respiratory assistance as needed, and treating or preventing complications of muscle weakness, is the only other option.

5.2 For populations 2 and 3: The submission appropriately nominated BSC as the comparator.

5.3 The submission also noted that there were two near market comparators:

- onasemnogene abeparvovec was considered at the November 2020 PBAC meeting for the treatment of paediatric patients aged less than 2 years with Type 1 SMA (subset of population 1); and
- nusinersen was considered for adult patients (>18 years of age) with SMA (population 3), also at the November 2020 PBAC meeting.

5.4 The proposed clinical management algorithm for risdiplam appropriately considered that nusinersen and risdiplam could be used sequentially for patients in population 1, but not in combination. However, the proposed clinical management algorithm assumed that all patients currently receiving BSC alone would initiate treatment with risdiplam.

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

6 Consideration of the evidence

Sponsor hearing

6.1 The sponsor requested a hearing for this item. The clinician noted that patients are interested in the efficacy of risdiplam but also consider that the route of administration is an important factor in clinical practice in terms of reducing the burden of treatment associated with intrathecal administration (headaches, complications from recurrent general anaesthetics, radiation from CT scans). In addition, the clinician noted that for patients who do not live near the hospitals that can administer nusinersen, the requirement to travel for treatment also imposed a heavy burden, which was exacerbated by the 2019/2020 summer bushfires and Covid-19 pandemic restrictions. The clinician noted that in practice, patients who had switched from nusinersen to risdiplam had done so on the basis of a preference for the route of administration.

6.2 The clinician considered that the ability to feed orally (associated with bulbar function) was an important outcome to patients and comorbidities associated with bulbar dysfunction have the greatest impact on hospitalisations and quality of life for younger patients and their carers. The clinician speculated that risdiplam may have additional benefits in bulbar function due to the systemic administration resulting in effect on cranial nerves.

6.3 The clinician noted that there was insufficient evidence to support concomitant use of nusinersen and risdiplam but considered that it would be appropriate for patients to switch from intrathecal injections to oral therapy if that is what they choose.

Consumer comments

6.4 The PBAC noted and welcomed the input from individuals (219), health care professionals (10) and organisations (4) via the Consumer Comments facility on the PBS website. The comments from individuals described the devastating impact of SMA on adult patients in terms of muscle pain and stiffness, inability to continue to work

and care for dependents and themselves, and inability to walk, eat, communicate and interact with the outside world.

6.5 The comments from individuals described a range of benefits of treatment with risdiplam including being a less invasive treatment option compared to nusinersen, and reducing the frequency of visits to specialist hospitals. Individual comments from adults who have used risdiplam noted improvements in symptoms or lack of deterioration. Adult patients who reported they would like to access risdiplam stated that they believed that risdiplam may slow progression of their disease or improve symptoms of SMA. The PBAC noted that a number of patient comments were received from patients aged 50 years and older, who were not able to access any treatment for SMA on the PBS.

6.6 The comments received by all organisations also highlighted the potential for risdiplam to effectively slow down the progression of muscle degeneration in adults with SMA. The organisational comments noted that it is important to adults with SMA to maintain function because as their condition continues to deteriorate, they will progressively lose their independence.

6.7 The PBAC noted the advice received from SMA Australia and Muscular Dystrophy Association of NSW supported the need for treatments for adults with SMA where there are no treatments presently available on the PBS.

6.8 The PBAC also noted the advice received from the National Paediatric Medicines Forum (NPMF) advocating for accessibility to risdiplam for paediatric patients to allow discontinuation of intrathecal administration with nusinersen. The NPMF considered the benefits of oral administration of risdiplam would include reducing radiation exposure through the CT scans required for each injection, and reduced hospital visits and painful intrathecal injections. The Muscular Dystrophy WA (MDWA) organisation also advocated for risdiplam as being a less invasive option compared to nusinersen as well as noting that parents/carers of young patients would be less likely to need to take time off work to travel to the specialist hospitals.

Clinical trials

6.9 Table 3 summarises the clinical evidence presented and how the trials were used to support the clinical claims in the submission.

Table 3: Summary of clinical evidence provided in the submission

Proposed population	Risdiplam	Nusinersen	Clinical evidence provided	Comment
Population 1				
≤18 years of age, SMA Type 1	FIREFISH Part 1 and Part 2	ENDEAR	MAIC for OS and EFS with FIREFISH (high dose cohort 1 pooled with cohort 2 ITT – single arm study) and ENDEAR (placebo controlled RCT), unanchored.	Naïve indirect comparison provided as sensitivity analysis.
≤18 years of age, SMA Types 2 and 3a	SUNFISH Part 2	CHERISH	MAIC for RULM with SUNFISH Part 2 (RCT) subset* and CHERISH (RCT) ITT, anchored	Not restricting patients to subgroup of patients ≤18 years in SUNFISH Part 2 may not be appropriate. Bucher indirect comparison and Bayesian NMA also provided as sensitivity analysis
Population 2				
≤18 years of age, SMA Type 3b	SUNFISH Part 2	N/A; BSC only	None provided	Only 6 patients in SUNFISH were assumed to have Type 3b SMA. There was a paucity of data for this population.
Population 3				
>18 years of age, SMA Types 1, 2 or 3	SUNFISH Part 2	N/A; BSC only	Direct RCT evidence for RULM and stabilisation of motor function from subgroup of patients aged 18-25 years enrolled in SUNFISH	Patients aged 18 are not part of population 3 and therefore may not be representative of the proposed population.^ Additionally, patients who are older than 25 years of age may also be treated under the proposed restriction. There were no patients with SMA Type 1 or Type 3 (ambulant) enrolled in SUNFISH Part 2, though it is unlikely that SMA Type 1 patients without access to a disease modifying treatment will survive till 18 years of age.

*subset includes only patients with age at screening ≤9, HFMSE baseline score ≥ 10 and no severe scoliosis
SMA = spinal muscular atrophy, MAIC = matching adjusted indirect comparison, OS= overall survival, EFS = event free survival, ITT = intention to treat, RULM = revised upper limb module, BSC = best supportive care, RCT = randomised controlled trial, NA = not applicable
^ The PSCR added that only 4 patients in the 18-25 age group were aged 18 years at the time of enrolment and all were in the risdiplam arm. The Sponsor did not consider it appropriate to examine a subgroup of a subgroup given the small number of patients (n=22).
Source: constructed during evaluation.

6.10 The submission also considered the following studies provide supportive evidence: For risdiplam – JEWELFISH (single arm safety study in 173 patients aged 2-60 years previously treated with other disease modifying treatments), and SUNFISH Part 1 in 51 patients aged 2-15 years (supportive safety evidence from pooled safety data), and for nusinersen – SHINE (an ongoing, open-label, non-comparative trial to evaluate the long-term safety, tolerability and efficacy in patients who participated in previous trials of nusinersen).

6.11 The PBAC previously considered the results of CHERISH in the November 2017 consideration of nusinersen for infantile onset (Type 1) and childhood-onset (Type 2 and 3) SMA, ENDEAR in the November 2017 consideration of nusinersen for infantile onset (Type 1) and childhood-onset (Type 2 and 3) SMA, and SHINE for the consideration of nusinersen in November 2017, July 2019 and July 2020.

6.12 Details of the trials and studies presented in the submission are provided in Table 4.

Table 4: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Randomised controlled trials		
SUNFISH Part 2	Primary Clinical Study Report – Study BP39055, SUNFISH. A two-part seamless, multicentre randomized, placebo-controlled, double blind study to investigate the safety, tolerability, pharmacokinetics, pharmacodynamics and efficacy of RO7034067 in Type 2 and 3 spinal muscular atrophy patients. Campbell C, Mercuri E, Baranello G et al. SUNFISH Part 1 results and Part 2 trial design in patients with type 2/3 spinal muscular atrophy (SMA) receiving risdiplam (RG7916).	Report No. 1099250, February 2020 Canadian Journal of Neurological Sciences 2019; 46: S31.
ENDEAR	Finkel R, Mercuri E, Darras B et al. Nusinersen versus Sham Control in Infantile-Onset Spinal Muscular Atrophy.	NEJM 2018; 377: 1723-1732.
CHERISH	Mercuri E, Darras B, Chiriboga C et al. Nusinersen versus Sham Control in Later-Onset Spinal Muscular Atrophy.	NEJM 2018; 378: 625-635
Primary non-randomised trials		
FIREFISH Parts 1 and 2	FIREFISH Part 2: Primary Clinical Study Report – Study BP39055, FIREFISH. A two-part seamless, open-label, multicentre study to investigate the safety, tolerability, pharmacokinetics, pharmacodynamics and efficacy of risdiplam in infants with Type 1 spinal muscular atrophy. Servais L, Baranello G, Masson R et al. FIREFISH Part 2: Efficacy and Safety of Risdiplam (RG7916) in Infants with Type 1 Spinal Muscular Atrophy (SMA) (1302).	Report No. 1100385. April 2020. Neurology 2020b; 94(15 Supplement):1302.
Supportive non-randomised trials and studies		
SUNFISH Part 1	Updated Clinical Study Report - Study BP39055, SUNFISH. A two-part seamless, multicentre randomized, placebo-controlled, double blind study to investigate the safety, tolerability, pharmacokinetics, pharmacodynamics and efficacy of RO7034067 in Type 2 and 3 spinal muscular atrophy patients. *Mercuri E, Baranello G, Kirschner J et al. SUNFISH part 1: 18-month safety and exploratory outcomes of risdiplam (RG7916) treatment in patients with type 2 or 3 spinal muscular atrophy (SMA).	Report No. 1101749. June 2020. Developmental Medicine and Child Neurology 2020;62: 56.
JEWELFISH	Interim Clinical Study Report – Study BP39055, FIREFISH. An open-label study to investigate the safety, tolerability, and	Report No. 1100549. June 2020.

Trial ID	Protocol title/ Publication title	Publication citation
	pharmacokinetics/pharmacodynamics of RO7034067 in adult and paediatric patients with spinal muscular atrophy. Chiriboga C, Mercuri E, Fischer D et al. JEWELFISH: Risdiplam (RG7916) increases survival of motor neuron (SMN) protein in patients with spinal muscular atrophy (SMA) that have previously received therapies targeting SMN2 splicing.	Developmental Medicine and Child Neurology 2019 ;61: 41-42.
Summary of clinical safety (Risdiplam)	Mercuri E , Bertini E, Chiriboga CA , et al. Pooled safety data from the risdiplam (RG7916) clinical trial development program.	SMA Europe - 2nd International Scientific Congress on Spinal Muscular Atrophy SMA-EU. 2020.
SHINE CS2/12	**Darras B, Chiriboga C, Iannaccone S et al. Nusinersen in later-onset spinal muscular atrophy: Long-term results from the phase 1/2 studies.	Neurology 2019; 92(21): e2492-e506.
SHINE-ENDEAR	**Castro D F, Farrar M. Nusinersen in infantile-onset spinal muscular atrophy: results from longer-term treatment from the open-label SHINE extension study.	American Academy of Neurology Annual Meeting 2020.
SHINE-CHERISH	**Chiriboga C. Longer-term treatment with nusinersen: results in later-onet spinal muscular atropy from the SHINE study. Mueller-Felber W, Darras B, Chiriboga C et al. Longer-term nusinersen treatment according to age at first dose: Results from the shine study in later-onset spinal muscular atrophy.	American Academy of Neurology Annual Meeting. 2020. European Journal of Neurology 2020; 27:221.
Pooled safety analysis (nusinersen)	**Darras BT, Farrar MA, Mercuri E et al. An Integrated Safety Analysis of Infants and Children with Symptomatic Spinal Muscular Atrophy (SMA) Treated with Nusinersen in Seven Clinical Trials.	CNS Drugs 2019d; 33(9): 919-32.

* SUNFISH Part 1 publications were identified in the risdiplam RCT search (Search 2), due to the 12 week RCT period at the start of the trial. It has been included in the master trials list as supportive evidence as the majority of the trial and longer-term follow up (after 12 weeks) is the non-randomised, single arm, open-label extension phase of the trial.
**Primary publication used for the purpose of the submission.
Source: Table 2.7, pp55-61 of the submission.

6.13 The key features of the included evidence are summarised in Table 5.

Table 5: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
Risdiplam single arm						
FIREFISH Part 1	21	OL, 12 mths	High	Type 1 SMA	OS, EFS, BSID-III, HINE-2, CHOP-INTEND	Not used
FIREFISH Part 2	41	OL, 24 mths*	High	Type 1 SMA	OS, EFS, BSID-III, HINE-2, CHOP-INTEND	Not used
Risdiplam vs. placebo						
SUNFISH Part 2	180	R, DB 12 mths	Low	Type 2 and 3 SMA non-ambulant	MFM32, RULM, HFMSE, SMAIS	Transitions between health states based on MFM32 and HFMSE
Nusinersen vs. placebo/sham-control						
ENDEAR	121	R, DB 13 mths	Low	Type 1 SMA	OS, EFS, HINE-2, CHOP-INTEND	Not used
CHERISH	126	R, DB, 15 mths	Low	Type 2 SMA	RULM,HFMSE, motor milestones	Not used

DB=double blind; OL=open label; OS=overall survival; EFS=event-free survival; R=randomised; MFM32 = motor function measures 32; RULM = revised upper limb module; HFMSE = hammersmith functional motor scale expanded; BSID-III = Bayley scales of infant and toddler development – third edition; CHOP-INTEND=children's hospital of Philadelphia infant test of neuromuscular disorders; HINE-2=hammersmith infant neurological examination module 2; SMAIS = SMA independence scale

*Primary endpoint analysed at 12 months

Source: compiled during the evaluation from Section 2 of the submission.

6.14 Sham procedure in ENDEAR (and CHERISH) consisted of a small needle prick on the lower back at the location where a lumbar puncture (LP) is normally made. The needle would break the skin but no LP or needle insertion occurred. The puncture would be covered with the same bandage used to cover LP injections normally, thus creating the appearance of an LP injection. Sedation and anaesthesia were not used for either LP or sham procedure in ENDEAR, but in CHERISH, if anaesthesia or sedation was to be used for LP procedures, minimal sedation (i.e. low dose of an anxiolytic) were used for the sham procedures.

6.15 For patients with SMA Type 1 in population 1, the clinical claim was based on an indirect treatment comparison (ITC) of risdiplam to nusinersen based on the results of overall survival (OS) and event free survival (EFS) in the single arm FIREFISH study (risdiplam only) and the ENDEAR RCT (nusinersen compared to sham-control) trials. A matching adjusted indirect comparison (MAIC) was presented. The submission stated that the outcome of EFS had a consistent definition across the risdiplam, nusinersen and natural history studies; defined as death or requiring ≥16 hours/day of non-invasive ventilation support for at least 14 days in the absence of acute reversible illness.

6.16 The proportion of infants sitting without support for 5 seconds at Month 12, as assessed in the gross motor subscale of BSID-III (Bayley scales of infant and toddler development – third edition) was the primary endpoint in FIREFISH, however this outcome measure was not used in the ITC undertaken by the submission. Instead the clinical claim was reasonably presented based on OS and EFS as the most patient relevant measures. The submission proposed that any change in OS or EFS favouring risdiplam should be considered clinically meaningful and to indicate non-inferiority. It was unclear if 'any increase' had to be statistically significant, and it may be unreasonable to not propose a magnitude of difference for the proposed minimum clinically important difference (MCID).

6.17 The submission stated that an acceptable non-inferiority margin for OS and EFS in SMA has not been published. Therefore, it was proposed that non-inferiority between risdiplam and nusinersen for OS be concluded if the point estimate of the hazard ratio in the ITC reported any benefit. Any assessment of non-inferiority should also consider the 95% confidence intervals obtained from the ITCs. Additionally, the submission claimed that any improvement over the natural history for EFS was clinically meaningful. It was unclear how this would apply to a comparison between risdiplam and nusinersen. As such, it may be inferred that no non-inferiority margin for EFS was proposed.

6.18 For patients with SMA Type 2 and 3 in population 1, the clinical claim was based on an ITC of risdiplam to nusinersen based on the results of the Revised Upper Limb Module (RULM) endpoint. Results for both the mean change from baseline RULM at 12 months, and proportion of patients with change from baseline ≥2 points for RULM at 12 months in the SUNFISH (risdiplam versus placebo) and CHERISH (nusinersen versus sham-control) trials were presented. Both MAIC and Bucher ITCs were presented. The submission proposed a non-inferiority margin of at least a score of zero change (lower margin) or 2 (upper margin), suggesting that this would be the MCID. The lower bound of the 95% confidence interval would be more appropriate for determining non-inferiority.

6.19 The RULM test is an outcome measure specifically developed to assess upper limb functional abilities in SMA patients (essential for non-ambulatory Type 3 adult patients to maintain a level of independence). The test assesses important aspects of upper limb function including the ability to drink from a cup, lift weighted items to and above, shoulder level, drawing, opening containers, switching on lights and reaching and manipulation. The submission stated that in the context of natural history data the mean change in RULM score was -0.4 in Type 2 and non-ambulant Type 3 patients aged 2.7 to 49.6 years (Pera 2019).

6.20 The motor function measure 32 (MFM32) is an ordinal scale that has the ability to assess a wide range of motor function across a broad range of SMA patients. The scale, which was the primary outcome in SUNFISH comprises 32 items that evaluate physical function in three dimensions. The scoring of each task uses a 4-point Likert scale based

on the patient's maximal abilities without assistance. The submission suggested that natural history data on patients aged 6 to 59 years, including Type 2 and Type 3 SMA patients, demonstrated an overall decline over time of -0.9 points per year in the MFM total score for Type 2 patients, and -0.6 for Type 3 patients (Vuillerot 2013a).

6.21 The Hammersmith functional motor scale expanded (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 change from baseline was the primary endpoint in the CHERISH trial. The scale contains 33 items, which are scored on a 3-point Likert-type scale and summed to derive the total score, with lower scores indicating greater impairment.

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

Comparative effectiveness

Population 1 ≤18 years of age, SMA Type 1

6.22 As no RCT was available for risdiplam in patients with SMA Type 1, the submission presented an unanchored MAIC to inform the comparative efficacy of risdiplam and nusinersen. The submission pooled the results from the high-dose cohort from FIREFISH Part 1 (n=17), where patients received the same dose as in Part 2, with patients in FIREFISH Part 2 (n=44) as this allowed for a greater sample size for risdiplam and was feasible given the similar trial designs between FIREFISH Part 1 and Part 2. Patients enrolled in FIREFISH had worse baseline children's hospital of Philadelphia infant test of neuromuscular disorders (CHOP-INTEND) and the Hammersmith infant neurological examination module 2 (HINE-2) scores compared to patients enrolled in ENDEAR, suggesting that patients enrolled in FIREFISH may have had more severe disease. Therefore, the submission used a propensity score logistic regression model to adjust for baseline characteristics, and this reduced the number of patients treated with risdiplam in FIREFISH from 58 patients to 36.5 patients. Matching was conducted on the variables of Type 1 SMA, age at first dose, duration of symptoms and baseline CHOP-INTED score. The baseline characteristics of patients before and after matching for FIREFISH and ENDEAR are presented in Table 6.

Table 6: FIREFISH baseline characteristics post ENDEAR-matching

Baseline characteristic	Pre-Matching: Risdiplam (Pooled FIREFISH)	Post-matching: Risdiplam (Pooled FIREFISH matching-adjusted to ENDEAR)	Nusinersen & BSC (ENDEAR)
Sample size (ESS)	58	58 (36.5)	121
Mean age at first dose in days	163 days	169 days	169 days
Female gender	57%	69%	55%
Mean age at symptom onset in days	51 days	55 days	60 days
Mean disease duration at screening in days	91 days	94 days	94 days
Mean age at diagnosis in weeks	12.7 weeks	14.3 weeks	14.3 weeks
Mean score on CHOP-INTEND	22.47	27.24	27.24
Mean HINE-2 score	0.93	1.28	1.37
Patients with ventilatory support	29%	18%	22%

CHOP-INTEND=Children's hospital of Philadelphia infant test of neuromuscular disorders; ESS=effective sample size; HINE-2=hammersmith infant neurological examination module 2
Source: Table 2.68, p166 of the submission.

6.23 The propensity matching resulted in reasonably balanced baseline characteristics between studies/trials, though the matching could not fully adjust for the proportion of females in FIREFISH compared to ENDEAR, and the post-matching population in FIREFISH had a lower proportion of patients with ventilator support than in ENDEAR, whereas FIREFISH had a higher proportion pre-matching.

6.24 Time to event analyses were conducted on the EFS and OS endpoints and hazard ratios were calculated based on a Cox proportional hazards model. Analyses were conducted using data at 12 months. The results of the MAIC for OS and EFS using FIREFISH and ENDEAR are presented in Table 7, together with the results of the naïve unadjusted ITC, presented as a sensitivity analysis.

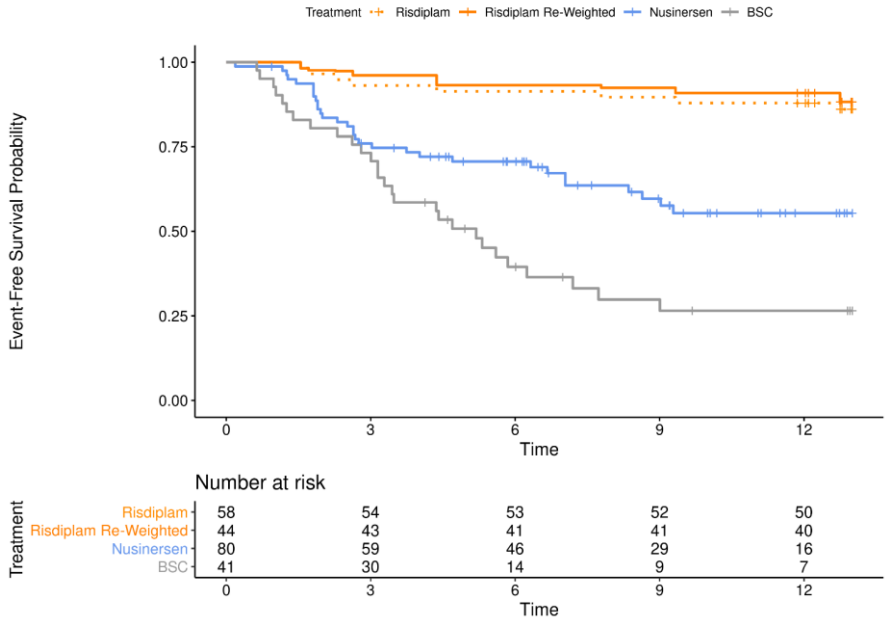
Table 7: Summary of results of the Type 1 SMA indirect comparison (FIREFISH and ENDEAR)

Study	Risdiplam n/N(%)	Sham-Control n/N(%)	Nusinersen n/N(%)	HR (95%CI)
EFS (events)				
FIREFISH (pre-match)	8/58 (13.8)	NA	NA	NA
FIREFISH (post-match)	5.12/44.42*	NA	NA	NA
ENDEAR	NA	28/41 (68.3)	31/80 (38.8)	0.53 (0.32, 0.89)
Risdiplam (pre-match) vs nusinersen (Naïve indirect)				0.244 (0.086, 0.462)
Risdiplam (post-match) vs nusinersen (MAIC)				0.197 (0.056, 0.415)
OS (events)				
FIREFISH (pre-match)	5/58 (8.6)	NA	NA	NA
FIREFISH (post-match)	2.34/44.42*	NA	NA	NA
ENDEAR	NA	16/41 (39.0)	13/80 (16.3)	0.37 (0.18, 0.77)
Risdiplam (pre-match) vs nusinersen (Naïve indirect)				0.442 (0.089, 1.020)
Risdiplam (post-match) vs nusinersen (MAIC)				0.261 (0.028, 0.665)

Event free survival defined as time to death or permanent ventilation (≥16 hours ventilation per day continuously for >21 days in the absence of an acute reversible event). *Pooled event data of patients from the 'High-dose' cohort (Cohort 2) of FIREFISH Part 1 (patients on pivotal dose selected for Part 2 of the study) and the ITT population of FIREFISH Part 2 (all patients enrolled in Part 2 of the study, regardless of whether they received treatment or not). HRs < 1 favour risdiplam.
* 44.42 is the sum of weights
CI=confidence interval; EFS= event free survival; HR=hazard ratio; OS=overall survival, NA = not applicable
Lower value for HR favours treatment with risdiplam
Source: Table 2.71, p169 of the submission, Finkel 2017

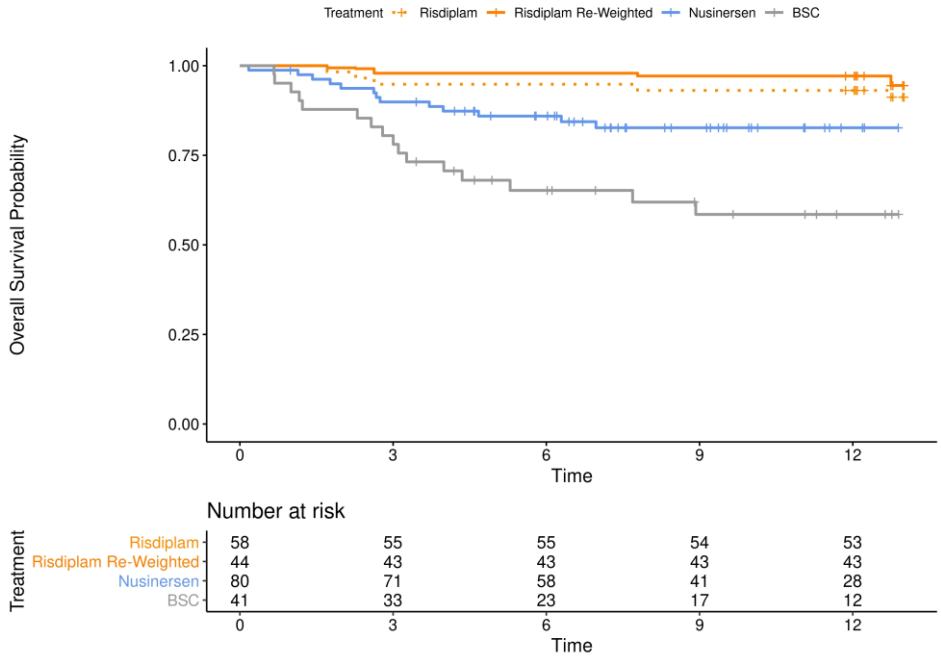
6.25 The EFS and OS Kaplan-Meier curves are presented in Figure 1 and Figure 2, respectively.

Figure 1: Event-free survival Kaplan-Meier curves for Type 1 SMA (FIREFISH and ENDEAR)



Event free survival defined as time to death or permanent ventilation (≥16 hours ventilation per day continuously for >21 days in the absence of an acute reversible event).
Source: Figure 2.38, p170 of the submission.

Figure 2: Overall survival Kaplan-Meier curves for Type 1 SMA (FIREFISH and ENDEAR)



BSC=best supportive care; OS=overall survival
Source: Figure 2.39, p171 of the submission.

6.26 While the results of the MAIC favoured risdiplam, the PBAC noted the following issues remained, rendering the results uncertain:

- FIREFISH had high risk of bias as it was single arm open-label study and;
- FIREFISH was a small study and the propensity matching reduced patient numbers even further.

<u>Population 1 ≤18 years of age, SMA Type 2 and 3a</u>

6.27 The submission presented two anchored MAICs for patients treated with risdiplam in SUNFISH Part 2 and with nusinersen in CHERISH using the outcomes of (i) RULM change from baseline and (ii) proportion of patients with a change in total RULM score of ≥2.

6.28 The submission stated that there were heterogeneity issues between SUNFISH Part 2 and CHERISH due to differences in enrolment criteria and baseline characteristics, as SUNFISH allowed enrolment of older and weaker patients with more progressed SMA disease compared to those enrolled in CHERISH. SUNFISH Part 2 included patients with SMA Type 2 and 3 (non-ambulant), whereas CHERISH enrolled only patients with SMA Type 2 (see Table 5). Therefore, the evaluation considered that while SUNFISH Part 2 included patients with more advanced disease, the disease progression of the entire cohort of patients in CHERISH may be more rapid, which may bias the ITC in favour of risdiplam when assessing results based on changes from baseline. The PSCR argued that it was clinically implausible that disease progression would be more rapid in

patients in CHERISH where mean age at symptom onset was similar. The PSCR maintained that patients enrolled in SUNFISH Part 2 were overall weaker compared to CHERISH and the difference was likely to bias the ITC results in favour of nusinersen. In addition, the PSCR noted that severe scoliosis and contractures (which can significantly impact a patient's movement and would be likely to impact on RULM measurement) was an exclusion criteria in CHERISH but patients with contractures were included in SUNFISH Part 2. The matching of patients was conducted only on a subset of patients in SUNFISH Part 2 who fulfilled the following criteria which were aligned with the inclusion and exclusion criteria of CHERISH:

- age at screening was 9 years or less, SUNFISH enrolled patients between ages 2 to 25. Patients over 18 years old were included in the data used to inform the efficacy of risdiplam in SUNFISH Part 2, whereas the analysis was used to inform the efficacy of using risdiplam in patients aged 18 years or less;
- baseline HFMSE score of 10 or more, SUNFISH enrolled patients irrespective of baseline HFMSE; and
- no severe scoliosis present at baseline.

This reduced the number of patients available for matching from 180 in the SUNFISH ITT population to 68 patients in the subset (43 in risdiplam and 25 in placebo).

6.29 In undertaking the MAIC, the submission used a propensity score logistic regression model to estimate the odds of a patient enrolled in SUNFISH Part 2 being enrolled into the CHERISH trial. Age at screening, SMN2 copy number and baseline motor function score were included as matching factors in Type 2 and 3 SMA.

6.30 The baseline characteristics of patients before and after matching for SUNFISH Part 2 and CHERISH are presented in Table 8.

Table 8: SUNFISH subset baseline characteristics pre and post CHERISH-matching (RULM endpoints)

Baseline characteristic	Pre-Matching (SUNFISH Part 2 subset°)		Post-matching (SUNFISH Part 2 subset° matching-adjusted to CHERISH)		Nusinersen & Sham (CHERISH)
	Risdiplam	Placebo	Risdiplam	Placebo	
Sample size (ESS)	43	25	43 (28.3)	25 (8.8)	121
Female gender	53%	44%	61%	43%	53%
Mean age at screening (years)	5.0	5.3	3.7	3.7	3.7 *
Mean age at symptom onset (months)	13.7	16.6	12.7	13.4s	10.3 *
Mean symptoms duration (months)	46.3	46.8	31.6	30.7	36.0*
Mean HFMSE baseline score	24.21	23.12	21.99	22.36	21.57
Mean RULM baseline score	21.65	22.28	19.11	19.07	19.07
Mean SMN2 copy number	3.09	3.08	3.00	2.94	2.94
% 2 copies	0%	4%	0%	7%	8%
% 3 copies	91%	84%	100%	91%	88%
% 4 copies	9%	12%	0%	1%	2%
% Unknown	0%	0%	0%	0%	2%

*In the absence of reported means, means for the overall CHERISH population were calculated as a weighted average of the medians for the purpose of these analyses.
°Patients from SUNFISH Part 2 aged ≤9 years at screening, with a HFMSE score ≥10 at baseline, and without severe scoliosis.
ESS=effective sample size; HFMSE=Hammersmith Functional Motor Scale Expanded; RULM=revised upper limb module; SMN=survival motor neuron
Source: Table 2.69, pp167-168 of the submission.

6.31 The propensity matching of SUNFISH Part 2 to CHERISH may not have been entirely successful. There were still differences in mean age of symptom onset (earlier in CHERISH), symptom duration (longer in CHERISH) and proportion of patients with two copies of SMN2 (higher in CHERISH). Given these are all considered to be prognostic and treatment effect modifiers by the submission, the evaluation considered that these differences in patient characteristics post matching likely biased the results of the MAIC, favouring risdiplam.

6.32 The results from the MAICs and the Bucher ITC for SUNFISH Part 2 and CHERISH are presented in Table 9 and Table 10.

Table 9: Indirect comparisons for RULM change from baseline at 12 months in patients aged ≤18 years with SMA type 2 and 3 (SUNFISH and CHERISH)

Comparator (study)	ESS/N	Change from baseline		Difference against control	Mean difference risdiplam against nusinersen (95% CI)
		Intervention	Control		
MAIC					
Risdiplam (SUNFISH subset°)	37.1/68	3.3	0.8	2.5	-0.49 (-3.33; 2.53)*
Nusinersen (CHERISH)**	126	3.7	0.7	3.0	Reference treatment
Bucher Indirect					
Risdiplam (SUNFISH subset°)	68	3.6	1.2	2.4	-0.60 (-2.24;1.22)*
Nusinersen (CHERISH)**	126	3.7	0.7	3.0	Reference treatment

°Patients from SUNFISH Part 2 aged ≤9 years at screening, with a HFMSE score ≥10 at baseline, and without severe scoliosis. *N=1000 successful bootstrap samples.**Extracted from the graph in Figure 2.27 of the submission using digitizing software: at 15 months the values were 4.2 for nusinersen and 0.5 for control (Table 2.44, p133 of the submission)
MAIC = matching adjusted indirect comparisonCI=confidence interval; ESS=effective sample size; N=number of samples; RULM=revised uppper limb module
Source: Source: Table 2.72, p173 and Table 2.74, p174 of the submission.

Table 10: Indirect comparisons for RULM responders (score change ≥ 2 points) at 12 months in patients aged ≤18 years with SMA type 2 and 3 (SUNFISH and CHERISH)

Comparator (STUDY)	ESS/N	Proportion of responders		OR against control	OR (95% CI)
		Intervention	Control		
MAIC					
Risdiplam (SUNFISH subset°)	37.1/68	88%	64%	4.1	2.64 (0; 117.94)*
Nusinersen (CHERISH) **	118	66%	56%	1.5	Reference treatment
Bucher Indirect					
Risdiplam (SUNFISH subset°)	68	79%	48%	4.1	2.66 (0.76; 12.74)*
Nusinersen (CHERISH) **	118	66%	56%	1.5	Reference treatment

°Patients from SUNFISH Part 2 aged ≤9 years at screening, with a HFMSE score ≥10 at baseline, and without severe scoliosis.
*N=1000 successful bootstrap samples.
** calculated from non-imputed data of RULM change from baseline at 12 months by the submission
CI=confidence interval; ESS=effective sample size; N=number of samples; OR=odds ratio; RULM= revised upper limb module
Source: Table 2.73, p 173 and Table 2.75, p174 of the submission.

6.33 There were no statistically significant differences observed between risdiplam and nusinersen, in either RULM outcome, in the MAIC and Bucher indirect comparisons.

6.34 The PBAC noted that there were significant issues with the MAIC presented for SUNFISH Part 2 and CHERISH, including:

- the submission's assertion that patients with severe contractures could not be reliably identified and removed from the SUNFISH subset to form a matched cohort with CHERISH patients;
- post matching characteristics such as symptom onset, duration and SMN2 copy number differed between groups and all favoured risdiplam;
- the outcomes from CHERISH were post-hoc estimates and may not be entirely accurate;
- there is the possibility of an unresolved exchangeability issue given that the proportion of patients who reported a change in RULM by ≥2 points in the post-matching placebo arm of SUNFISH Part 2 (64%) was higher than the sham control arm in CHERISH (56%) and almost as high as the nusinersen arm in CHERISH (66%); and
- the matching of patients resulted in significant loss of statistical power due to sample size reduction from SUNFISH Part 2, and neither SUNFISH Part 2 nor CHERISH were powered to detect differences in RULM.

6.35 The Bucher ITC showed comparable efficacy results to the MAIC. However, the PBAC noted that given the multiple transitivity issues between SUNFISH Part 2 and CHERISH, the results of the Bucher indirect comparison should also be interpreted with caution. For both the MAIC and the Bucher ITC for patients with Type 2 and 3 SMA, it did not appear that the submission excluded patients with Type 3b SMA or patients who commenced treatment at 19 years of age or more, and therefore the results were not entirely applicable to patients in population 1.

6.36 The PBAC noted the limitations of the MAIC and Bucher ITC as identified above. On balance, the PBAC considered that it was reasonable to conclude that risdiplam

appears to be non-inferior to nusinersen for patients ≥18 years of age with SMA Type 2 and 3a.

Population 2 ≤18 years with SMA Type 3b

6.37 The PBAC noted that no clinical evidence was specifically provided by the submission to support the efficacy or safety of risdiplam in patients with SMA Type 3b. It was noted that only 6 patients (3 in each treatment arm) enrolled in SUNFISH Part 2 could have been diagnosed as SMA Type 3b.

Population 3 >18 years with SMA Type 1, 2, or 3

6.38 To support the use of risdiplam in patients in population 3, the submission provided efficacy outcomes of risdiplam versus BSC for patients aged 18 to 25 years from the SUNFISH Part 2 trial. The PBAC noted the very small patient numbers (n=22) for this cohort.

6.39 A summary of these outcomes is provided in Table 11. Outcomes for other age groups in the trial were also provided in the submission.

Table 11: Summary of results in the pre-specified subgroup of ages 18 - 25 years in SUNFISH Part 2

Age Group 18 - 25 years	Risdiplam (N=14)	Placebo (N=8)
Change from baseline in MFM32 Total Score at Month 12		
Number of patients at baseline	14	8
Mean MFM32 at baseline (SD)	40.25 (10.75)	48.96 (13.86)
MFM32 MMRM change from baseline at Week 52 [a] (SE)	-1.01 (1.04)	-0.36 (1.36)
95% CI	(-3.06, 1.04)	(-3.04, 2.32)
MMRM difference (SE)	-0.65 (1.71)	
95% CI	(-4.03, 2.74)	
p-value	0.7072	
Proportion of MFM32 Responders at Month 12		
Number of patients at baseline	14	8
Responders (MFM32 change ≥0)	8 (57.1%)	3 (37.5%)
Odds ratio for overall response (95% CI)	2.12 (0.35, 12.81)	
p-Value	0.4118	
Change from baseline in RULM Total Score at Month 12		
Number of patients at baseline	14	8
Mean RULM at baseline (SD)	18.36 (6.82)	21.63 (9.72)
RULM MMRM change from baseline at Week 52 [a] (SE)	1.06 (0.85)	-0.68 (1.13)
95% CI	(-0.63, 2.74)	(-2.90, 1.55)
MMRM difference (SE)	1.74 (1.41)	
95% CI	(-1.06, 4.53)	
p-value	0.2219	
Proportion of RULM Responders at Month 12		
Number of patients at baseline	14	8
Responders (RULM change ≥0)	11 (78.6%)	3 (37.5%)
Odds ratio for overall response (95% CI)	5.79 (0.84, 39.72)	
p-Value	0.0740	
Change from baseline in SMAIS Caregiver Reported Total Score at Month 12		
Number of patients at baseline	13	8
Mean SMAIS at baseline (SD)	27.00 (10.24)	29.63 (12.95)
Number of patients at Week 52	13	8
Mean SMAIS at week 52 (SD)	26.77 (9.34)	26.25 (12.58)
SMAIS mean change from baseline at Week 52 (SD)	-0.23 (3.72)	-3.38 (1.41)
95% CI	(-2.48, 2.02)	(-4.55, -2.20)
Mean difference (95%CI) [a]	3.15 (0.44, 5.86) [b]	
Change from baseline in SMAIS Patient Reported Total Score at Month 12		
Number of patients at baseline	14	8
Mean SMAIS at baseline (SD)	28.79 (8.29)	32.00 (11.05)
Number of patients at Week 52	14	8
Mean SMAIS at week 52 (SD)	29.21 (9.73)	30.88 (12.14)
SMAIS mean change from baseline at Week 52 (SD)	0.43 (3.13)	-1.13 (3.83)
95% CI	(-1.38, 2.24)	(-4.33, 2.08)
Mean difference (95%CI) [a]	1.56 (-1.39, 4.51)	
Change from baseline in HFMSE total score at Month 12		
Number of patients at baseline	14	8
Mean HFMSE at baseline (SD)	9.79 (9.45)	16.88 (15.61)
Number of patients at Week 52	14	8
Mean HFMSE* at week 52 (SD)	9.14 (9.55)	16.38 (15.27)
HFMSE* mean change from baseline at Week 52 (SD)	-0.64 (1.69)	-0.50 (0.76)
95% CI	(-1.62, 0.33)	(-1.13, 0.13)
Mean difference (95%CI) [a]	-0.14 (-1.38, 1.11)	

CI=confidence interval; MFM32=motor function measure - 32 items; MMRM=mixed model repeated measures; RULM=revised upper limb module; SD= standard deviation; SE=standard error; SMAIS= SMA independence scale
* Text indicates values extracted or calculated during evaluation
[a] Calculated during evaluation using StatsDirect v3.3.4
[b] Likely to not be statistically significant after adjusting for multiple testing in SUNFISH Part 2
Source: Table 2.64, pp157-158 of the submission, p685, Primary SUNFISH CSR.

6.40 A statistically significant difference (based on lower 95% confidence interval of mean difference exceeding zero) was reported only for the outcome of SMAIS caregiver reported change in total score, which favoured treatment with risdiplam. After adjusting for multiple testing, it was likely that the result for caregiver reported SMAIS was not statistically significantly different between treatment arms in the subgroup of patients aged 18-25 years in SUNFISH Part 2, as was observed for the ITT population. No other motor score outcome appeared to be statistically significantly different between treatment arms, even before adjustment for multiple testing.

6.41 The PBAC noted that the results from the submission's subgroup analysis may not be representative of the efficacy of risdiplam in population 3 for the following reasons:

- patients aged 18 years were included in the analysis but are not part of population 3,
- no patients aged >25 years were included in the analysis but patients who are older than 25 years of age may be treated under the proposed restriction (e.g. JEWELFISH enrolled patients up to 60 years of age and a number of patients who submitted consumer comments reported that they were aged 50 or over); and
- there were no patients with SMA Type 1 or Type 3 (ambulant) enrolled in SUNFISH Part 2, though it is unlikely that patients with SMA Type 1 who have not had access to disease modifying treatment survive until 18 years of age.

6.42 The PSCR identified that there were 4 patients aged 18 in the 18-25 year cohort and all were in the risdiplam arm and also noted that at baseline, no patients were in the "standing" state and a single patient in the placebo arm was in the "walking" state.

Comparative harms

6.43 No head to head clinical trials for risdiplam and nusinersen were identified. As such, there was limited information on the comparative harms for risdiplam and nusinersen. The submission presented a MAIC and network meta-analysis (NMA) on the broad safety outcomes for 'Any adverse event', 'Any adverse event leading to discontinuation' and 'Any serious adverse event' in FIREFISH and ENDEAR (at up to 6 months), as well as an indirect comparison and NMA for the outcome of 'serious adverse events' in SUNFISH Part 2 and CHERISH.

6.44 For the FIREFISH versus ENDEAR indirect comparison for safety, the base case analysis suggested that risdiplam may be associated with fewer AEs leading to discontinuation and any serious adverse events compared to nusinersen in both the naïve comparison and MAIC analysis. However, this was not a reliable comparison as the indirect comparisons also implausibly concluded that treatment with risdiplam was associated

with fewer AEs leading to discontinuation and any serious adverse events compared to treatment with sham-control in ENDEAR (which was a small needle prick as described in paragraph 6.14). The difference observed between FIREFISH and ENDEAR may instead be due to the difference in trial design between FIREFISH (single arm open label) and ENDEAR (double blinded RCT), or heterogeneity in the patients enrolled.

6.45 For the SUNFISH versus CHERISH safety comparison, in the Bucher ITC, Bayesian NMA and the anchored MAIC, the reporting of serious AEs was higher for risdiplam treated patients in a comparable SUNFISH Part 2 subset, compared to nusinersen treated patients in CHERISH. However, as the 95% confidence intervals for the ORs included values <1, it was concluded that the analyses could not differentiate between the two treatments. Given the transitivity issues between SUNFISH and CHERISH described in paragraph 6.35, the results of the ITC for safety were also likely to be unreliable. However, it was noted that the safety results from the indirect comparison between SUNFISH and CHERISH do not support the safety results of FIREFISH and ENDEAR as described in paragraph 6.45.

6.46 Overall, the indirect comparisons for safety outcomes between risdiplam and nusinersen were inconclusive and subject to a high degree of bias (in unknown directions) and uncertainty. Nonetheless, given the less invasive route of administration of risdiplam compared to nusinersen, the PBAC considered that the conclusion that risdiplam has a favourable safety profile in some patients may be reasonable, noting that the safety profiles are different.

6.47 Direct head to head safety data for risdiplam compared to BSC was available from SUNFISH Part 2. In SUNFISH Part 2, risdiplam had a higher rate of diarrhoea compared with placebo (16.7% and 8.3% respectively) which was not statistically significant. The incidence of serious adverse events (SAE) was comparable between treatment arms in SUNFISH (risdiplam, 20%; placebo, 18.3%). The most common SAE in SUNFISH was pneumonia (risdiplam 7.5% vs placebo, 1.7%) which was not statistically significantly different between treatment arms. The submission noted that all pneumonia cases resolved despite ongoing treatment with risdiplam after 4-21 days and were considered as unrelated to risdiplam. The PBAC considered the submission's claim of inferior but manageable adverse events with risdiplam versus BSC was supported by the direct head to head results for SUNFISH Part 2.

Benefits/harms

6.48 The comparisons presented in the submission did not allow for a quantitative comparison of the benefits and harms of risdiplam and nusinersen or of risdiplam and BSC. Accordingly, a benefits/harms table has not been presented.

Clinical claim

Population 1

6.49 For population 1, the submission claimed that risdiplam is non-inferior to nusinersen in terms of efficacy and safety, with a favourable safety profile in some patients due to differences in administration (oral versus intrathecal).

- For patients with SMA Type 1, while the results of the MAIC and naïve ITC were considered to be highly uncertain, the results for OS and EFS strongly favoured risdiplam over nusinersen, and therefore the claim may be reasonable, despite no non-inferiority margins being proposed, and the uncertainties identified in the ITC. The PBAC considered that the claim of non-inferior efficacy in this population was reasonable based on the evidence.

- For patients with SMA Type 2 and 3a, the commentary considered the claim of non-inferior efficacy was not supported, as non-inferiority could not be concluded based on the various indirect comparisons of SUNFISH and CHERISH. Additionally, there were significant issues with the MAIC between SUNFISH Part 2 and CHERISH presented, suggesting that the comparison presented had a high degree of uncertainty. Noting these issues with the MAIC and the limited data available, the PBAC agreed with the ESC that the claim of non-inferiority was not well-supported by the evidence in this population, however PBAC considered that, on balance, risdiplam is likely to have efficacy that is comparable to nusinersen for patients with SMA Type 2 and 3a.

6.50 With regards to comparative safety, the ITCs for safety outcomes between risdiplam and nusinersen were inconclusive and subject to a high degree of bias (in unknown directions) and uncertainty. Nonetheless, given the less invasive route of administration of risdiplam compared to nusinersen the PBAC considered that the conclusion that risdiplam has a favourable safety profile in some patients was reasonable.

Populations 2 and 3

6.51 For patients in populations 2 and 3, the submission claimed that risdiplam is superior to BSC in terms of efficacy, and inferior in terms of safety, with minimal treatment-related adverse events that are clinically manageable.

- For population 2, the PBAC considered that the claim of superior comparative effectiveness versus BSC was not adequately supported as the submission did not present any data to demonstrate the efficacy and safety versus BSC specifically for patients with SMA Type 3b.

- For population 3, the PBAC considered that the claim of superior comparative effectiveness versus BSC was not adequately supported as the evidence showed that there were no statistically significant differences for any of the efficacy

outcomes, except for caregiver reported SMAIS in the SUNFISH Part 2 trial of risdiplam versus BSC (which was unlikely to be statistically significant once multiple testing was adjusted for) in the subgroup of patients aged 18 to 25 years from SUNFISH Part 2. The data presented to support efficacy in population 3 was also not entirely applicable to the requested population due to differences in age.

- The PBAC considered that the claim of inferior but manageable adverse events with risdiplam compared to BSC was supported by the safety results of the ITT population in SUNFISH Part 2 for patients in populations 2 and 3.

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

Economic analysis

6.52 The submission presented a cost-utility analysis of risdiplam versus BSC for patients in population 3, and a cost-minimisation analysis of risdiplam versus nusinersen for patients in population 1. An economic evaluation was not specifically presented for patients in population 2, for whom the nominated comparator was BSC, but the submission claimed that the cost minimisation in population 1 and the cost effectiveness in population 3 would apply to population 2. The PBAC considered that this was not sufficiently justified, as the disease progression of patients with Type 3b SMA (population 2) would be significantly different to those with Type 1 or 2 SMA aged under 18 years (parts of population 1) and Type 1 or 2 SMA who were aged over 18 years (parts of population 3).

Cost utility analysis (population 3)

6.53 As the PBAC considered the claim for superior efficacy of risdiplam over BSC in population 3 was not supported by the clinical evidence, the cost-utility analysis in this population was not considered to be informative.

6.54 A summary of the key components of the economic model for population 3 is presented in Table 12.

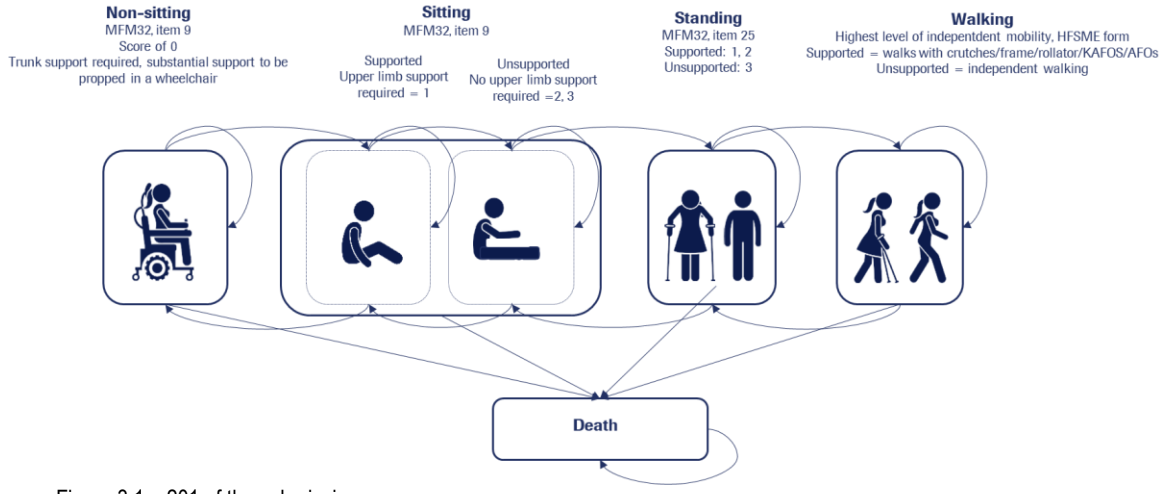
Table 12: Key components of the economic evaluation

Component	Description	Justification/comments
Type of analysis	Stepped cost-utility analysis	The PBAC considered the claim of superior efficacy in population 3 was not supported by the evidence.
Steps	1. Trial based (12 mths) 2. Extrapolate to lifetime 3. Incorporate MRU	The submission also included two extra steps (incorporate adverse event costs and convert to utility) but were unnecessary as no adverse event costs were considered and utility was used as the outcome from Step 1.
Outcomes	Life years gained and cost per quality-adjusted life years	
Time horizon	Lifetime (62 years)	The submission claimed this was consistent with published economic evaluations.
Methods used to generate results	Markov	
Health states	6 health states: Non-sitting Sitting supported Sitting unsupported Standing Walking Death	The ESC noted that it was unclear whether the data from SUNFISH Part 2 could inform these health states appropriately.
Cycle length	Monthly	Given that MFM32 was assessed every 4 months in SUNFISH, this may not be appropriate, but is unlikely to have a large impact.
Transition probabilities	RCT data from SUNFISH Part 2	The ESC noted that the transition probabilities between the health states were highly uncertain due to the very small patient numbers in SUNFISH Part 2 for the 18-25 year age group cohort (n=22). The ESC considered that the transition probabilities may be inappropriate as there did not appear to be statistically significantly differences observed in SUNFISH regarding the MFM32 items between treatment arms.
Software package	Excel 2016	

MRU = medical resource use, mths = months
Source: Table 3.2, p197 ant Table 3.3, p198 of the submission.

6.55 The structure of the economic model is presented in Figure 3.

Figure 3: Structure of economic model



Source: Figure 3.1, p201 of the submission

6.56 The health states used in the economic model were determined by the scores from the motor function measure 32 (MFM32) or Hammersmith functional motor scale expanded (HFMSE) in SUNFISH Part 2, based on the following:

- Not sitting – MFM32 Item 9 score = 0
- Sitting supported – MFM32 item 9 score = 1
- Sitting unsupported – MFM32 item 9 score = 2 or 3
- Standing – MFM32 item 25 score = 1-3
- Walking – HFSME form – highest level of independent mobility (item unknown)

6.57 A continuous time multi state model (MSM) using raw data from the ≥12 year old subgroup in SUNFISH Part 2 was used by the submission to calculate the probability of moving between health states each cycle (month).

6.58 Patients started in any health state except non-sitting, based on the baseline distribution of MFM32 scores of the subgroup of patients aged ≥12 years in SUNFISH. In each monthly cycle, patients could die (based on pooling of six natural history studies for SMA Type 2 and Australian lifetables for SMA Type 3) and if they survived, they could improve, worsen or remain in the same health state based on probabilities estimated by a continuous time multi-state model (MSM) fitted to data from SUNFISH. The ESC noted that the probability of death was the same in both treatment arms in the model, but the transition probabilities between other health states were dependent on the treatment arm.

6.59 Patients in the risdiplam arm were assumed to remain on risdiplam until death in the base case, and accrued the related drug costs each cycle. Patients in the BSC arm did not receive any intervention costs, but there were costs associated with each health state that were derived from a combination of a UK burden of illness conducted by the Sponsor and Chambers 2020.

6.60 There were no patients who started in the 'not sitting' health state in either the placebo or risdiplam arm, and only one patient in the 'standing' health state in the risdiplam arm who did not transition to any state, so the reliability of the MSM for any probabilities from the 'not sitting' or 'standing' health states were highly uncertain. Additionally, there were very few patients to inform the MSM to begin with, adding more uncertainty. None of the transition intensity hazard ratios for risdiplam versus placebo were statistically significantly different (consistent with the clinical evidence described in Table 11), therefore it may not have been appropriate to have assumed any differences for transition between health states between the two treatment arms.

6.61 The ESC noted that the magnitude of difference in transition probabilities between treatment arms was minor (<6% in all transitions, and <2% in most cases), which partly explains the high ICER in the model, as treatment with risdiplam did not result in significant improvement in patient outcomes, and treatment with risdiplam was not always beneficial.

6.62 Health state utilities were informed by results from the EQ-5D from SUNFISH Part 1 and 2. Additionally, in the submission's base case, a carer utility was included which was derived from Baranello 2019, a discrete choice experiment (DCE) of UK caregivers commissioned by the Sponsor. The PBAC guidelines v5 (p65) state that consideration beyond the patient should be presented as a supplementary analysis in addition to the base case, which should include outcomes that are associated with the patient (only). The ESC noted that the evaluation appropriately excluded caregiver utilities in the base case ICERs (unless otherwise specified). Both costs and utility were discounted at 5% per annum, though inappropriately, discounting was applied from cycle 2 onwards as opposed to after the first year of the model.

6.63 The submission identified a range of possible utility values which may have informed the economic evaluation. These are presented in Table 13.

Table 13: Utility values used in the economic evaluation

Health state	Base case	Alternative sources of utility			
	SUNFISH Part 1 and 2 pooled EQ-5D AU tariff [a]	SUNFISH part 2 EQ-5D AU tariff [a]	Lloyd 2019	NICE ERG TA588	HUI NatHis data
Not sitting	0.273 [b]	0.302 [b]	0.080	0.040	0.4877
Sitting (supported)	0.273 [b]	0.302 [b]	0.080	0.040	0.5389
Sitting (unsupported	0.341	0.358	0.140	0.100	0.5389
Standing	0.427	0.415 [c]	0.390	0.390	0.5646
Walking	0.493	0.415 [c]	0.720	0.720	0.8373

[a] Utility from SUNFISH includes health state utility from the trial plus baseline utility which was added to all patients aged >12 years i.e. the whole cohort

[b] Not sitting and sitting supported pooled due to small sample size

[c] Standing and walking pooled due to small sample size

Cells shaded grey indicate values applied in base case of model

EQ-5D = EurQol-5 dimensions, AU = Australia, NICE = National Institute for Health and Care excellence ERG = evidence review group

Source: Table 3.14, p215-216, Table 3.15, p216 and 3.16, p217 of the submission

6.64 The submission argued that as there were ambulatory patients enrolled in SUNFISH Part 1 but not in SUNFISH Part 2, using the SUNFISH Part 1 and 2 pooled utilities was a more precise estimate of the utility in the 'walking' health state. However, using pooled utilities from SUNFISH Part 1 and 2 but efficacy/transition data from the subgroup of patients aged ≥12 years in SUNFISH Part 2 was an inconsistent approach and may have biased the economic model in favour of risdiplam. The ESC noted that the choice of utility values appears to be a key driver of the model, and sensitivity analysis using the SUNFISH Part 2 utilities increased the ICER by 36% whereas using utilities from Lloyd 2019 decreased the ICER by 41%..

6.65 The key drivers of the model identified during the evaluation are summarised in Table 14.

Table 14: Key drivers of the model

Description	Method/Value	Impact
Transition probabilities	Based on a continuous time multi-state model (MSM) fitted to data from a subgroup of patients who were aged 12-25 years in SUNFISH Part 2. There were very few data points to inform transitions, and transitions which were not statistically significant were modelled.	High. Favours risdiplam as it was assumed that patients treated with risdiplam were more likely to improve and less likely to worsen in most health states. Using 'NatHis' study to inform BSC then applying SUNFISH Part 2 ITT HR increased ICER by 93%.
Utilities	Based on pooled SUNFISH Part 1 and Part 2 EQ-5D data. Additionally, data from risdiplam and BSC arms were inappropriately pooled together, which favours risdiplam as any disutilities associated with adverse events from risdiplam treatment were, inappropriately, partially attributed to patients treated with BSC. The submission identified several other sources of utilities, and it was unclear which would be the most suitable for the base case.	High, but given the large number of possible sources of utility the direction of bias was unclear. For example, using utility from just SUNFISH Part 2 increased the ICER by 36%, but using utility from Lloyd 2019 decreased the ICER by 41%.

Source: Constructed during evaluation.

6.66 The results of the economic evaluation, excluding carer spill-over utilities, are presented in Table 15.

Table 15: Results of the stepped economic evaluation

Step and component	Proposed medicine	Comparator	Increment
Step 1: trial-based costs and outcomes (time horizon 1 year)			
Costs	$[redacted]	$0	$[redacted]
QALY gained	0.2559	0.2532	0.0027
Incremental cost/extra QALY gained			$[redacted][1]
Step 2: time horizon extended to 62 years, discounted			
Costs	$[redacted]	$0	$[redacted]
QALY	4.3846	4.1665	0.2180
Incremental cost/extra QALY gained			$[redacted][1]
Step 3-5: include health state costs			
Costs	$[redacted]	$985,164	$[redacted]
QALY	4.3846	4.1665	0.2180
Incremental cost/extra QALY gained			$[redacted][1]

Text in italics indicate values calculated during evaluation (Removed discounting from year 1 and excluded carer utilities)
Source: Constructed during evaluation using Economic Evaluation_Population 3.xlsm.
The redacted values correspond to the following ranges:
[1] *> $1,055,000/QALY gained*

6.67 The ESC noted that the base case ICER presented by the submission was > $1,055,000/QALY when considering patient utility only. The > $1,055,000/QALY quoted by the submission included 'spill-over' utility to caregivers, which effectively doubled the QALY gain (0.218 to 0.399).

6.68 A range of univariate sensitivity analyses were conducted during the evaluation, including variations around extrapolation functions, the price of risdiplam and utility

sources (Table 16). The ESC noted that in no reasonable scenario did the ICER fall below > $1,055,000/QALY.

Table 16: Results of sensitivity analyses conducted during the evaluation

Analyses	Incremental cost	Incremental QALY	ICER	Percent change
Base case	**$** [redacted]	**0.2180**	**$** [redacted][1]	**NA**
Using NatHis transition probabilities and applying SUNFISH Part 2 ITT HR (base case SUNFISH Part 2 ≥12 years)	$ [redacted]	0.113	$ [redacted][1]	+92.67%
Including Belter 2018 for OS estimates (base case: exclude Belter 2018) – Gompertz functional form[a]	$ [redacted]	0.230	$ [redacted][1]	-0.70%
Change OS functional form to Weibull (base case Gompertz)	$ [redacted]	0.218	$ [redacted][1]	+0.10%
Change OS functional form to Generalised Gamma (base case Gompertz)	$ [redacted]	0.218	$ [redacted][1]	+0.07%
Change utility based on SUNFISH Part 2 (base case SUNFISH Part 1 and part 2 pooled)	$ [redacted]	0.161	$ [redacted][1]	+35.82%
Change utility based on Lloyd 2019 (base case SUNFISH Part 1 and Part 2 pooled)	$ [redacted]	0.367	$ [redacted][1]	-40.56%
Reduce cost of risdiplam by 50%	$ [redacted]	0.218	$ [redacted][1]	-50.98%

[a] Based on eff_SMATypeII_Survival.pptx
Source: Constructed during the evaluation.
The redacted values correspond to the following ranges:
[1] >$1,055,000/QALY gained

6.69 The ESC considered that the economic model had limited value in informing cost-effectiveness considerations due to the lack of evidence of a benefit of treatment in this population. The ESC considered that even with highly optimistic assumptions and acknowledging the clinical need for new therapies for patients in this population, the ICERs for the model presented were very high based on the requested price for risdiplam. The PSCR acknowledged the limitations of the available data in population 3 and the challenge to demonstrate cost-effectiveness for this population. The PSCR also reiterated the clinical need for effective treatment to halt or slow progression of disability resulting from SMA in this patient population and expressed a willingness to work with PBAC to enable PBS subsidy for risdiplam for these patients.

<u>Cost minimisation (population 1)</u>

6.70 The submission proposed different approaches to calculation of the published and effective prices for risdiplam for population 1.

6.71 For the cost-minimisation analysis the proposed basis for calculation of equi-effective doses for the effective price for risdiplam was: 5 mg of risdiplam daily is equi-effective to nusinersen 12 mg (5 mL) every 4 months (i.e. excluding nusinersen loading doses).

6.72 The proposed basis for calculation of equi-effective doses for the published price for risdiplam was: 5 mg of risdiplam daily is equi-effective to nusinersen 12 mg (5 mL) administrations 6 administrations in Year 1, and 3 administrations from Year 2 onwards; over a time horizon of 5 years.

Table 17: Results of the proposed cost-minimisation analysis for published prices

Component	Risdiplam	Nusinersen
Cost per dose	$13,010.27/12 = $1,084.19	$110,000
Dose frequency	Daily	4 monthly
Administrations	7 per week	3 loading doses + 3 maintenance doses in year 1 3 maintenance doses per year in years 2-5
Total medicine cost year	$396,000	$660,000 during year 1 and $330,000 during years 2 to 5
Medicine cost per unit	$13,010.27 per 60mg bottle	$110,000 per 12mg injection **
Difference in cost per year in year 1	Risdiplam = -$264,000 (due to loading doses)	
Difference in cost per year during years 2-5	Risdiplam = +$66,000	
Cost per year averaged years 1 to 5	Risdiplam = $396,000, Nusinersen = $396,000	
Cost per administration every 4 months, including loading doses	$0	$1,505
Overall difference in cost per year averaged over 5 years	Risdiplam = -$27,090 ($1,505*5)	

Source: Cost-minimisation analysis CMA worksheet.

6.73 The cost of loading doses and administration for nusinersen were included in the cost-minimisation analysis, in order to demonstrate the potential cost savings associated with the use of risdiplam in population 1, though these costs were not proposed to be included in the calculation of the effective price for risdiplam, which was based on maintenance doses of both treatments only. The calculation also assumed that all patients treated with risdiplam would require the highest dose of 5 mg per day. The ESC considered that this approach was appropriately conservative.

6.74 The ESC noted that the listing of risdiplam for population 1 on the basis proposed in the submission may be overall cost-saving as:

- the cost for the administration of nusinersen was not included in the calculation of price parity;
- price parity was appropriately sought without including the cost for the loading doses of nusinersen required in the first year for patients initiating treatment, lowering the overall cost of nusinersen treatment; and
- the daily dose of risdiplam assumed (5 mg) was likely an overestimate as there would be a number of paediatric patients who weigh less than 20 kg (and would require a lower dose while they remain less than 20 kg).

Drug cost/patient/month: $33,000 (published price)

6.75 The ESC noted that based on a dose of 5 mg per day, which was a potential overestimate of the dose required for risdiplam, the submission estimated a cost of $33,000 per patient per month, assuming no discontinuations and no wastage, based on the published price of nusinersen. In the financial estimates, the submission assumed that incident patients would receive a dose of 1.5 mg per day for the first year, and 5 mg per day thereafter.

Estimated PBS usage & financial implications

6.76 This submission was not considered by DUSC.

6.77 The submission used an epidemiological approach to estimate the PBS usage of risdiplam, whereby the incident population was based on a birth prevalence of 8.66 per 100,000 as reported from 1 year of data from the newborn screening programs in NSW and the ACT by Kariyawasam 2020. However, the submission appears to have erroneously assumed a birth prevalence of 10 per 100,000 in the calculation of incident patient numbers, using the birth prevalence of 8.66 per 100,000 for prevalent patients only. Distribution of SMA type was informed by data from Verhaart 2017, where proportional rates were reported to be 5.5/9.1 (60%) for SMA Type 1, 1.9/9.1 (21%) for SMA Type 2, and 1.7/9.1 (19%) for SMA Type 3, with the submission making no allowance for any patients to have SMA Type 4. Of the 19% of patients with SMA Type 3, the submission estimated that 88.5% would have SMA Type 3a, and 11.5% SMA Type 3b based on the proportions in the SUNFISH Part 2 trial.

6.78 Prevalent patients were estimated by applying survival curves to each SMA type, and the calculated number of prevalent patients were added to 'Year 0' incident (new) cases to derive the total eligible patient population.

6.79 Overall, it was not clear how applicable the estimates would be, given that incidence rates can vary over time (as noted in country specific data reported by Verhaart 2017) and also since incidence detection may increase if newborn screening of SMA becomes more common Australia wide, and given that other sources such as Arkblad 2009 report a different distribution of SMA patients.

6.80 As discussed in paragraph 3.3, there may be potential for use outside of the proposed and recommended populations, specifically, in pre-symptomatic treatment and patients with SMA Type 4.

6.81 The number of patients to be treated with risdiplam under the proposed listing and the corresponding financial impact based on the published price is shown in Table 19 below.

Table 19: Estimated use and financial implications across all patient populations using published prices

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Population 1 treated	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Population 2 treated	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Population 3 treated	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Number of patients treated [a]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Number of scripts dispensed [b]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
Estimated financial implications of risdiplam [c]						
Net PBS/RPBS cost Pop 1	$[redacted][3]	$[redacted][4]	$[redacted][4]	$[redacted][5]	$[redacted][6]	$[redacted][7]
Net PBS/RPBS cost Pop 2	$[redacted][9]	$[redacted][9]	$[redacted][9]	$[redacted][9]	$[redacted][9]	$[redacted][9]
Net PBS/RPBS cost Pop 3	$[redacted][5]	$[redacted][6]	$[redacted][6]	$[redacted][7]	$[redacted][8]	$[redacted][8]
Cost to PBS/RPBS	$[redacted][7]	$[redacted][8]	$[redacted][10]	$[redacted][11]	$[redacted][12]	$[redacted][12]
Copayments	–$[redacted][9]	–$[redacted][9]	–$[redacted][9]	–$[redacted][9]	–$[redacted][9]	–$[redacted][9]
Cost to PBS/RPBS less copayments	$[redacted][7]	$[redacted][8]	$[redacted][10]	$[redacted][11]	$[redacted][12]	$[redacted][12]
Estimated financial implications for nusinersen [c]						
Cost to PBS/RPBS less copayments	$[redacted][5]	$[redacted][5]	$[redacted][6]	$[redacted][6]	$[redacted][7]	$[redacted][8]
Net financial implications*						
Net PBS/RPBS cost Pop 1 (include nusinersen offset)	-$[redacted][3]	-$[redacted][3]	-$[redacted][3]	-$[redacted][3]	-$[redacted][3]	-$[redacted][9]
Net PBS/RPBS cost Pop 2	$[redacted][9]	$[redacted][9]	$[redacted][9]	$[redacted][9]	$[redacted][9]	$[redacted][9]
Net PBS/RPBS cost Pop 3	$[redacted][5]	$[redacted][6]	$[redacted][6]	$[redacted][7]	$[redacted][8]	$[redacted][8]
Net cost to PBS/RPBS	**$**[redacted][4]	**$**[redacted][5]	**$**[redacted][5]	**$**[redacted][6]	**$**[redacted][7]	**$**[redacted][8]
Net cost to MBS [d]	$[redacted][9]	$[redacted][9]	$[redacted][9]	$[redacted][9]	$[redacted][9]	$[redacted][9]
Net cost to PBS/RPBS/MBS budgets	**$**[redacted][4]	**$**[redacted][5]	**$**[redacted][5]	**$**[redacted][6]	**$**[redacted][7]	**$**[redacted][8]

Pop = population

[a] May be different to sum of each population due to rounding

[b] Assuming for incident patients, 4.57 scripts (1 bottle each script) being required for the first 6 months, and a remaining 4.57 scripts (1 bottle each script) required for the continuing scripts for the following 6 months, and for prevalent patients, 10.15 scripts (3 bottles each script) per year. No discontinuation of nusinersen or risdiplam was assumed. There were no incident patients assumed in population 3

[c] Based on the published price of risdiplam and nusinersen. Offset only applies to patients in population 1

[d] additional doctor visits (MBS item 105, 100% fee $44.35, but 85% rebate applied)

[e] cost of nusinersen administrations avoided. Based on DRG B767B.

Source: Table 4.3, pp236-237, and Tables 4.34, 4,41, 4,42, pp258-262 of the submission.

The redacted values correspond to the following ranges:

[1] <500

[2] 500 to < 5,000

[3] $10 million to < $20 million

[4] $20 million to < $30 million

[5] $30 million to < $40 million

[6] $40 million to < $50 million

[7] $50 million to < $60 million

[8] $60 million to < $70 million

[9] $0 to < $10 million

[10] $70 million to < $80 million

[11] $90 million to < $100 million

[12] $100 million to < $200 million

6.82 For populations 1, 2 and 3 the submission estimated a total cost of $200 million to < $300 million over the first six years of listing using the published price for risdiplam. For population 1 only, the submission estimated a net saving for the PBS/RPBS over

the first six years of listing based on published prices, with additional cost offsets for hospital health budgets due to nusinersen administration costs avoided.

6.83 Cost savings in population 1 were due to the cost of loading doses of nusinersen not being considered as part of the cost minimisation to determine the effective price of risdiplam (as described in paragraph 6.73). As the submission's cost offset for nusinersen was only applicable for patients in population 1, there was a net cost to the PBS/RPBS driven predominantly by the cost of treating patients in population 3, since the submission estimated that there would only be a few patients in population 2 (estimated to be 5-10 patients per year).

6.84 The ESC considered that the estimated utilisation of risdiplam may be underestimated for the following reasons:

- For patients in population 1, the ESC noted that the submission's financial estimates did not consider patients currently not receiving nusinersen (i.e. treated with BSC) who were eligible for treatment with risdiplam and did not consider that the availability of an oral formulation was likely to grow the market. The ESC considered that market growth could be substantial given that nusinersen needs to be administered in a specialist centre by intrathecal administration, and given that risdiplam can be administered orally, with specialist centres not specified in the proposed restriction(s). The PSCR noted that clinicians report that most eligible patients are being treated.

- Contrary to the proposed clinical management algorithm, in which the submission suggested that risdiplam would completely replace BSC in populations 2 and 3, in the financial estimates it was assumed that only 50%-90% of patients in population 2 and 50%-75% of prevalent patients in population 3 who are currently being treated with BSC would be treated with risdiplam. The ESC noted that for population 2 and 3, DUSC previously considered that uptake might approach 100% of incident and prevalent patients (Nusinersen Public Summary Document (PSD), Nov 2017, para 6.60), and at the present time, there are no treatments specifically available on the PBS for patients in populations 2 and 3. The ESC considered that the uptake in population 3 was uncertain and may be underestimated due to strong patient interest in accessing treatment that they consider may slow progression of symptoms.

- The submission only considered patients born after 1975. Given that patients with SMA Type 3 have a normal life expectancy, it was likely that this approach would have underestimated the number of patients with SMA Type 3 in population 3 who may be eligible for treatment with risdiplam. The ESC agreed with the commentary that this may significantly underestimate the number of eligible patients given there may be patients who are older than 45 years of age with SMA Type 3 who are likely to want to access treatment to risdiplam if they consider that it may reduce

the progression of their symptoms. The PBAC noted that the consumer comments confirmed that this was the case.

- Grandfathered patients were assumed to have been captured in the submission's estimate of patient numbers. The PBAC noted that it was not clear whether this was reasonable. The PSCR noted that the Sponsor is currently providing compassionate access to 7 patients with Type 1 SMA and expects approximately 20 patients with Type 2 SMA to start treatment on the program in due course.

6.85 The submission's financial estimates in population 1 and 2 may have been overestimated as the submission assumed that a rate of 10 per 100,000 live births to be diagnosed with SMA, instead of the 8.66 per 100,000 reported in Kariyawasam 2020, which slightly overestimated use in incident patients.

6.86 The ESC agreed with the evaluation that overall, it was likely that the number of patients predicted to be treated with risdiplam, and therefore the financial estimates, were underestimated, even though there were assumptions made by the submission which may counterbalance the estimates.

6.87 The financial estimates were sensitive to the assumed diagnostic rate. Changing the number of cases per 100,000 live births in the sensitivity analysis had a substantial impact on the financial estimates, with a doubling of the incidence rate more than doubling the expected cost to the PBS based on published prices. The incidence rate may be higher than assumed in the submission if newborn screening becomes widely adopted in Australia, and there was variance in the incidence rates reported in literature.

Financial Management – Risk Sharing Arrangements

6.88 While the submission did not propose a subsidisation cap, the Sponsor stated that they were willing in principle to enter the existing nusinersen Deed for population 1, and willing to explore opportunities in order to progress the listing for risdiplam for patients in population 2 and population 3.

6.89 The ESC noted that the PSCR proposed [redacted] The PSCR stated that this may be achievable through savings associated with risdiplam compared with nusinersen and would allow access to effective treatment for this small population (estimated to be around 6 patients per year, though up to 20 were expected to be enrolled in compassionate access programs). The PBAC considered that [redacted] required accepting the same level of cost-effectiveness for population 2. The PBAC considered this was not reasonable due to the lack of any clinical evidence in this patient population.

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

7 PBAC Outcome

Population 1 (≤18 years of age, SMA Type 1, 2 or 3a)

7.1 The PBAC recommended the listing of risdiplam (Evrysdi®) for patients with Spinal Muscular Atrophy (SMA) Types 1, 2 or 3a who are aged 18 years or under at treatment initiation, on the basis that it should be available only under special arrangements under Section 100. The PBAC's recommendation for listing was based on, among other matters, its assessment, as described above, that the cost-effectiveness of risdiplam would be acceptable if it were cost-minimised against nusinersen.

7.2 The PBAC's recommendation was based on equi-effective doses of 5 mg of risdiplam daily and nusinersen 12 mg (5 mL) per administration every 4 months (3 per year, i.e. excluding nusinersen loading doses).

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 the sponsor hearing and consumer comments, risdiplam has advantages in reducing the treatment burden for patients in terms of potential pain, stress or complications from the intrathecal administration (lumbar puncture) procedure and also in reducing the need for patients to travel to specialist hospitals for administration of treatment.

7.4 The PBAC noted that the proposed restriction would need to be revised to reflect the population for whom PBS listing was recommended (population 1). The PBAC noted that the proposed restriction, appropriately does not allow concomitant use of risdiplam with other disease modifying treatments for SMA. The PBAC noted that flow-on changes would be required for the nusinersen listings to prevent concomitant treatment with risdiplam. The PBAC noted no restrictions on previous disease modifying treatments were proposed. The PBAC considered that for patients who had previously been treated with nusinersen, a wash out period may be required when swapping therapy to risdiplam. The PBAC considered it appropriate that decisions about a washout periods should be at the clinical judgement of the prescriber. The PBAC considered it appropriate that decisions about a washout periods should be at the clinical judgement of the prescriber. The PBAC considered that it would be appropriate for patients diagnosed with symptomatic type I, II or IIIa spinal muscular atrophy, who are eligible for continuing therapy with nusinersen, to be able to swap therapy to risdiplam without requiring prescribers to resubmit the initial evidence of eligibility. The PBAC also considered that it would be appropriate for eligible patients to swap therapy from risdiplam to nusinersen, should a clinician deem it appropriate. The PBAC foreshadowed that if additional disease modifying treatments for SMA are listed on the PBS further consideration may need to be given to restrictions regarding their use prior to risdiplam.

7.5 The PBAC accepted nusinersen as the appropriate comparator for risdiplam for population 1 in the submission.

7.6 The PBAC noted that as no RCT was available for risdiplam in patients with SMA Type 1, the submission presented an unanchored MAIC for patients in FIREFISH and ENDEAR to inform the comparative efficacy of risdiplam and nusinersen. The PBAC noted that the baseline characteristics were reasonably well-balanced after propensity matching and the results for OS and EFS strongly favoured risdiplam over nusinersen. The PBAC noted the results of the MAIC were uncertain and had a high risk of bias as FIREFISH was a small single arm open-label study. Overall the PBAC considered the evidence in this population sufficiently supported the claim of non-inferior efficacy.

7.7 The PBAC noted that anchored MAICs were presented for patients with SMA Type 2 and 3a for the point estimate of RULM change and the proportion of RULM responders from SUNFISH Part 2 and CHERISH. However significant transitivity issues existed between the trial populations and the MAIC was not completely successful in matching patients including across some factors that would be predictive of outcomes. The PBAC noted that for the point estimate of RULM non-inferiority was not well-supported based on the results of the MAIC but that the comparison of RULM responders numerically favoured risdiplam. The PBAC noted the limitations of the MAIC and the inherent lack of precision in the confidence estimates for the indirect comparisons (where there the trial populations were small) and on balance, the PBAC considered that it was reasonable to conclude that risdiplam appears to be non-inferior to nusinersen for patients ≤18 years of age with SMA Type 2 and 3a.

7.8 The PBAC noted that although there was no direct comparison of safety between risdiplam versus nusinersen, given the less invasive route of administration of risdiplam compared to nusinersen the PBAC considered that the conclusion that risdiplam has a favourable safety profile in some patients was reasonable.

7.9 The PBAC noted that the submission's cost minimisation analysis assumed that all patients treated with risdiplam would require the highest dose of 5 mg per day and did not include costs for nusinersen loading doses or administration costs. The PBAC considered that this approach was appropriate, even though conservative, given the limitations of the available evidence for risdiplam and nusinersen and the treatment costs.

7.10 The PBAC noted that the sponsor indicated an in-principle willingness to share the existing nusinersen caps for population 1. The PBAC noted that the sponsor's financial estimates for population 1 assumed there would be no patients currently unable or unwilling to receive nusinersen and that patients currently on compassionate access programs (7 Type 1 SMA patients) would be captured in the submission's patient estimates. The PSCR stated that clinicians report most eligible patients are being treated. The PBAC noted that the submission estimated that risdiplam would be cost saving to the PBS/RPBS on the basis of reduced loading doses for nusinersen, the PBAC noted that this was uncertain. Therefore the PBAC considered that it was appropriate

that risdiplam be included in the existing RSA for nusinersen for this population and that there would be no basis for increasing the existing caps.

7.11 The PBAC recommended that risdiplam should be treated as interchangeable on an individual patient basis with nusinersen.

7.12 The PBAC advised that risdiplam is not suitable for prescribing by nurse practitioners.

7.13 The PBAC recommended that the Early Supply Rule should apply.

7.14 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because risdiplam is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over nusinersen, or not expected to address a high and urgent unmet clinical need given the presence of an alternative therapy, the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2009* for Pricing Pathway A were not met.

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

Populations 2 (≤18 years of age, Type 3b SMA) and 3 (>18 years, Type 1, 2 or 3 SMA)

7.16 The PBAC did not recommend the listing of risdiplam for: patients with Type 3b SMA aged 18 years or under at treatment initiation (population 2); or for patients with SMA Types 1, 2 or 3 aged over 18 years at treatment initiation (population 3).

7.17 The PBAC considered that the submission did not provide evidence demonstrating a clinical benefit for risdiplam in population 2 and the evidence for population 3 did not demonstrate that risdiplam delays or prevents progression in these patients. Therefore the cost-effectiveness of risdiplam compared with best supportive care (BSC) in these populations could not be determined.

7.18 The PBAC acknowledged the clinical need for effective treatments in the adult patient population with SMA, where there are currently no treatments available on the PBS to delay the progression of muscular degeneration in adults with SMA of any type. The PBAC noted that many of the consumer comments focused on the importance of maintaining independence and the ability to work and communicate for adult SMA patients.

7.19 The PBAC accepted that BSC was the appropriate comparator for risdiplam in populations 2 and 3 where there currently are no PBS listed treatments.

7.20 The PBAC noted that no clinical evidence was specifically provided by the submission to support the efficacy or safety of risdiplam in patients with SMA Type 3b (population 2). Only 6 patients (3 in each treatment arm) enrolled in SUNFISH Part 2 could have been diagnosed as SMA Type 3b.

7.21 The PBAC noted that evidence for risdiplam in patients in population 3 was based on efficacy outcomes of risdiplam versus BSC for patients aged 18 to 25 years from the

SUNFISH Part 2 trial. The PBAC noted the very small patient numbers (n=22) for this cohort. Overall, the PBAC noted the SUNFISH Part 2 trial was underpowered and did not demonstrate statistically significant differences for the efficacy outcomes, with the possible exception of caregiver reported SMAIS. The data presented to support efficacy in population 3 was also not entirely applicable to the requested population due to the inclusion of patients aged 18 and exclusion of patients older than 25 years. For population 3, the PBAC considered that the claim of superior comparative effectiveness versus BSC was not adequately supported by the data presented.

7.22 The PBAC considered the clinical claim that risdiplam would be inferior in terms of safety compared to BSC but with manageable adverse effects was reasonable, supported by the safety results of the ITT population in SUNFISH Part 2 for patients in populations 2 and 3.

7.23 The PBAC noted that there was no economic evaluation presented for population 2 due to the absence of any standalone clinical evidence for that population. The PSCR proposed [redacted]. The PBAC considered that this approach required accepting the same level of cost-effectiveness for population 2 as for population 1. The PBAC considered this was not reasonable due to the lack of any clinical evidence in this patient population.

7.24 As the PBAC considered the claim for superior efficacy of risdiplam over BSC in population 3 was not supported by the clinical evidence, the cost-utility analysis in this population was not informative. Further, the PBAC noted that applying the clinical trial data from the subgroup in SUNFISH Part 2 in the economic model, where no statistically significant differences in outcomes were demonstrated, resulted in highly uncertain cost-effectiveness estimates. The PBAC noted that without the caregiver utility included, the model estimated a small benefit for risdiplam (0.218 QALYs over the 62 year time horizon). The PBAC noted that this reflected the clinical data used to inform the model, but it was not consistent with the expectations expressed in the consumer comments regarding the potential QoL benefit associated with risdiplam treatment for adult patients.

7.25 The PBAC noted that the base case ICER presented by the submission was > $1,055,000/QALY when considering patient utility only. The PBAC noted that in no reasonable scenario considered in the sensitivity analyses did the ICER fall below > $1,055,000 /QALY. The PBAC considered that even in the context of the high clinical need for disease modifying treatments for adult patients to halt or slow progression of disability resulting from SMA, the ICERs for the model presented were very high based on the requested price for risdiplam. The PSCR acknowledged the limitations of the available data in population 3 and the challenge to demonstrate cost-effectiveness for this population. In its pre-PBAC response the sponsor expressed an openness to suggestions and collaboration to enable PBS subsidy for risdiplam for these patients. However, the PBAC considered that, in the submission presented, the sponsor did not

provide sufficient basis for acceptance of the cost-effectiveness of risdiplam in populations 2 and 3.

7.26 The PBAC considered that the financial estimates for populations 2 and 3 were uncertain and may be underestimated because (1) the uptake in population 3 appears to be underestimated due to strong patient interest in accessing treatment and (2) the submission estimates only considered patients born after 1975.

7.27 The PBAC noted that as part of a decision at the November 2020 meeting, a stakeholder meeting for treatments related to SMA was held in December 2020 which included the sponsor of risdiplam. The PBAC had recommended, it was in the interests of patients and families, prescribers and payers for a decision support analysis for SMA treatment that takes into account all the currently available clinical data and informs a broader "whole of disease" economic and financial analyses.

7.28 The PBAC noted that work with Australian clinicians will continue in an effort to progress the available evidence in this population based on clinical experience and registry data.

7.29 The PBAC considered a resubmission for risdiplam should address the lack of evidence to support the efficacy of risdiplam in populations 2 and 3. The resubmission may be lodged at any future standard due date for PBAC submissions using the standard re-entry pathway.

Outcome:
Recommended for patients ≤18 years of age at treatment initiation, with SMA Type 1, 2 or 3a.

8 Recommended listing

8.1 Add new items:

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
RISDIPLAM					
risdiplam 750 microgram/mL powder for oral liquid, 80 mL	NEW (Public) TMP04177 NEW (Private) TMP04178	1	1	0	Evrysdi
		Max.Qty multiplier = 3, Repeat increase: 0			

Concept ID (for internal Dept. use)	**Category / Program:** Section 100 – Highly Specialised Drugs Program (Public/Private hospitals code)
	Prescriber type: ☒Medical Practitioners
	Restriction Type ☒Authority Required – non-immediate/delayed assessment by Services Australia
	Episodicity: Symptomatic
	Severity: Type I, II or IIIa
	Condition: Spinal muscular atrophy (SMA)

26577	**Indication:** Symptomatic Type I, II or IIIa spinal muscular atrophy (SMA)
	Treatment Phase: Initial treatment
26575	**Clinical criteria:**
26573	The condition must have genetic confirmation of 5q homozygous deletion of the survival motor neuron 1 (SMN1) gene; or
26574	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
22123	**Clinical criteria**
22122	Patient must have experienced at least two of the defined signs and symptoms of SMA type I, II or IIIa prior to 3 years of age
	AND
22077	**Clinical criteria:**
22076	The treatment must be given concomitantly with best supportive care for this condition
	AND
27580	**Clinical criteria:**
NEW CC1 27579	The treatment must not be in combination with PBS-subsidised treatment with nusinersen for this condition
	AND
22104	**Clinical criteria:**
22103	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
27587	**Treatment criteria:**
NEW 27586	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.
22083	**Population criteria:**
22082	Patient must be 18 years of age or under
22084 22085 22086	**Prescribing Instructions:** Defined signs and symptoms of Type I SMA are: i) Onset before 6 months of age; and ii) Failure to meet or regression in ability to perform age-appropriate motor milestones; or iii) Proximal weakness; or iv) Hypotonia; or v) Absence of deep tendon reflexes; or vi) Failure to gain weight appropriate for age; or vii) Any active chronic neurogenic changes; or viii) A compound muscle action potential below normative values for an age-matched child. Defined signs and symptoms of Type II SMA are: i) Onset between 6 and 18 months of age; and ii) Failure to meet or regression in ability to perform age-appropriate motor milestones; or iii) Proximal weakness; or iv) Weakness in trunk righting/derotation; or v) Hypotonia; or vi) Absence of deep tendon reflexes; or vii) Failure to gain weight appropriate for age; or viii) Any active chronic neurogenic changes; or ix) A compound muscle action potential below normative values for an age-matched child. Defined signs and symptoms of Type IIIa SMA are: i) Onset between 18 months and 3 years of age; and

	ii) Failure to meet or regression in ability to perform age-appropriate motor milestones; or iii) Proximal weakness; or iv) Hypotonia; or v) Absence of deep tendon reflexes; or vi) Failure to gain weight appropriate for age; or vii) Any active chronic neurogenic changes; or viii) A compound muscle action potential below normative values for an age-matched child.
22105	**Prescribing Instructions:** Invasive permanent assisted ventilation means ventilation via tracheostomy tube for greater than or equal to 16 hours per day.
26600 FULL	**Prescribing Instructions:** Application for authorisation of initial treatment must be in writing 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) specification of SMA type (I, II or IIIa); and (ii) sign(s) and symptom(s) that the patient has experienced; and (iii) patient's age at the onset of sign(s) and symptom(s).
25744 CAR flag	**Administrative Advice:** Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au, Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos, Or mailed to: Services Australia, Complex Drugs, Reply Paid 9826, HOBART TAS 7001
7607	**Administrative Advice:** No increase in the maximum number of repeats may be authorised.
7608	**Administrative Advice:** Special Pricing Arrangements apply.

MEDICINAL PRODUCT **medicinal product pack**	**PBS item code**	**Max. qty packs**	**Max. qty units**	**№.of Rpts**	**Available brands**
RISDIPLAM					
risdiplam 750 microgram/mL powder for oral liquid, 80 mL	NEW (Public) TMP04179 NEW (Private) TMP04180	1	1	5	Evrysdi
		Max.Qty multiplier = 3, Repeat increase: 0			

Concept ID (for internal Dept. use)	**Category / Program:** Section 100 – Highly Specialised Drugs Program (Public/Private hospitals code)
	Prescriber type: ☒Medical Practitioners
	Restriction Type ☒Authority Required – immediate/real time assessment by Services Australia (telephone/online)
26577	**Indication:** Symptomatic Type I, II or IIIa spinal muscular atrophy (SMA)
	Treatment Phase: Continuing treatment
~~11365~~	**Clinical criteria:**

NEW 27600	
11364 27599	Patient must have previously received PBS-subsidised treatment with this drug for this condition OR Patient must be eligible for continuing PBS-subsidised treatment with nusinersen for this condition.
	AND
27580	**Clinical criteria:**
NEW CC1 27579	The treatment must not be in combination with PBS-subsidised treatment with nusinersen for this condition
	AND
22104	**Clinical criteria:**
22103	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
	AND
22077	**Clinical criteria:**
22076	The treatment must be given concomitantly with best supportive care for this condition
27587	**Treatment criteria:**
NEW 27586	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.
22105	**Prescribing Instructions:** Invasive permanent assisted ventilation means ventilation via tracheostomy tube for greater than or equal to 16 hours per day.
	AND
NEW 27609	**Prescribing Instructions:** 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.
25745 CAR flag	**Administrative advice:** Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).
7607	**Administrative Advice:** No increase in the maximum number of repeats may be authorised.
7608	**Administrative Advice:** Special Pricing Arrangements apply.

Grandfather

MEDICINAL PRODUCT **medicinal product pack**	**PBS item code**	**Max. qty packs**	**Max. qty units**	**№.of Rpts**	**Available brands**
RISDIPLAM					
risdiplam 750 microgram/mL powder for oral liquid, 80 mL	NEW (Public) TMP04181 NEW (Private) TMP04182	1	1	0	Evrysdi
		Max.Qty multiplier = 3, Repeat increase: 0			

Concept ID (for internal Dept. use)	**Category / Program:** Section 100 – Highly Specialised Drugs Program (Public/Private hospitals code)
	Prescriber type: ☒Medical Practitioners
	Restriction Type – ☒Authority Required – non-immediate/delayed assessment by Services Australia
26577	**Indication:** Symptomatic Type I, II or IIIa spinal muscular atrophy (SMA)
	Treatment Phase: Transitioning from non-PBS to PBS subsided treatment – 'Grandfather' treatment

26575	**Clinical criteria:**
26573	The condition must have genetic confirmation of 5q homozygous deletion of the survival motor neuron 1 (SMN1) gene; or
26574	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
22123	**Clinical criteria:**
22122	Patient must have experienced at least two of the defined signs and symptoms of SMA type I, II or IIIa prior to 3 years of age
	AND
~~24453~~ 27602	**Clinical criteria:**
~~24452~~ NEW 27601	Patient must have previously received non-PBS subsidised treatment with this drug for this condition prior to 1 August 2021.
	AND
27583	**Clinical criteria:**
New CC3 27582	Patient must not be receiving invasive permanent assisted ventilation in the absence of a potentially reversible cause while being treated with this drug
	AND
27580	**Clinical criteria:**
NEW CC1 27579	The treatment must not be in combination with PBS-subsidised treatment with nusinersen for this condition
	AND
NEW 27604	**Clinical criteria:**
27603	The treatment must be given concomitantly with best supportive care for this condition
	AND
27608	**Clinical criteria:**
27606	Patient must be responding to non-PBS subsidised risdiplam for this condition at the time of application
	AND
27587	**Treatment criteria:**
New TC1 27586	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.
27596	**Population criteria:**
New GFPC1 27595	Patient must have been 18 years of age or under at the time non-PBS subsidised treatment with this drug was initiated for this condition
26600 FULL	**Prescribing Instructions:** Application for authorisation of initial treatment must be in writing 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) specification of SMA type (I, II or IIIa); and (ii) sign(s) and symptom(s) that the patient has experienced; and (iii) patient's age at the onset of sign(s) and symptom(s).
22084 22085 22086	**Prescribing Instructions:** Defined signs and symptoms of Type I SMA are: i) Onset before 6 months of age; and ii) Failure to meet or regression in ability to perform age-appropriate motor milestones; or iii) Proximal weakness; or iv) Hypotonia; or v) Absence of deep tendon reflexes; or

	vi) Failure to gain weight appropriate for age; or vii) Any active chronic neurogenic changes; or viii) A compound muscle action potential below normative values for an age-matched child. Defined signs and symptoms of Type II SMA are: i) Onset between 6 and 18 months of age; and ii) Failure to meet or regression in ability to perform age-appropriate motor milestones; or iii) Proximal weakness; or iv) Weakness in trunk righting/derotation; or v) Hypotonia; or vi) Absence of deep tendon reflexes; or vii) Failure to gain weight appropriate for age; or viii) Any active chronic neurogenic changes; or ix) A compound muscle action potential below normative values for an age-matched child. Defined signs and symptoms of Type IIIa SMA are: i) Onset between 18 months and 3 years of age; and ii) Failure to meet or regression in ability to perform age-appropriate motor milestones; or iii) Proximal weakness; or iv) Hypotonia; or v) Absence of deep tendon reflexes; or vi) Failure to gain weight appropriate for age; or vii) Any active chronic neurogenic changes; or viii) A compound muscle action potential below normative values for an age-matched child.
25744 CAR flag	**Administrative Advice:** Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au, Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos, Or mailed to: Services Australia, Complex Drugs, Reply Paid 9826, HOBART TAS 7001
~~20162~~ NEW 27528	**Prescribing Instructions**: A patient may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a Grandfathered patient must qualify under the Continuing treatment criteria.
25398	**Administrative Advice**: This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria.
7607	**Administrative Advice:** No increase in the maximum number of repeats may be authorised.
7608	**Administrative Advice:** Special Pricing Arrangements apply.

Flow-on changes:

For nusinersen items 11363C, 11378W, 11472T, 11476B (for treatment of patients with symptomatic Type 1, 2 or 3a SMA) add clinical criterion as follows:

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
NUSINERSEN					
nusinersen 12mg/5ml injection, 5ml vial	11363C (Pub) 11472T (Priv)	1	1	3	Spinraza

Concept ID	
(for internal Dept. use)	**Category / Program:** Section 100 – Highly Specialised Drugs Program (Public/Private hospitals code)
	Prescriber type: ☒Medical Practitioners
	Restriction Type ☒Authority Required – non-immediate/delayed assessment by Services Australia
	Episodicity: Symptomatic
	Severity: Type I, II or IIIa
	Condition: Spinal muscular atrophy (SMA)
26577	**Indication:** Symptomatic Type I, II or IIIa spinal muscular atrophy (SMA)
Edit	**Treatment Phase:** Initial treatment - Loading doses
22093	**Clinical criteria:**
22094	Must be treated by a specialist medical practitioner experienced in the diagnosis and management of SMA associated with a neuromuscular clinic of a recognised hospital in the management of SMA; or in consultation with a specialist medical practitioner experienced in the diagnosis and management of SMA associated with a neuromuscular clinic of a recognised hospital in the management of SMA
	AND
26575	**Clinical criteria**
26573	The condition must have genetic confirmation of 5q homozygous deletion of the survival motor neuron 1 (SMN1) gene; or
26574	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
22123	**Clinical criteria:**
22122	Patient must have experienced at least two of the defined signs and symptoms of SMA type I, II or IIIa prior to 3 years of age
	AND
27598	**Clinical criteria:**
Insert New 27597	The treatment must not be in combination with PBS-subsidised treatment with risdiplam for this condition
	AND
22077	**Clinical criteria:**
22076	The treatment must be given concomitantly with standard of care for this condition
	AND
22079	**Clinical criteria:**
22080	The treatment must not exceed four loading doses (at days 0, 14, 28 and 63) under this restriction
	AND
22083	**Population criteria:**
22082	Patient must be 18 years of age or under
22084 22085 22086	Prescribing Instructions: Defined signs and symptoms of type I SMA are: i) Onset before 6 months of age; and ii) Failure to meet or regression in ability to perform age-appropriate motor milestones; or iii) Proximal weakness; or iv) Hypotonia; or v) Absence of deep tendon reflexes; or

	vi) Failure to gain weight appropriate for age; or vii) Any active chronic neurogenic changes; or viii) A compound muscle action potential below normative values for an age-matched child. Defined signs and symptoms of type II SMA are: i) Onset between 6 and 18 months; and ii) Failure to meet or regression in ability to perform age-appropriate motor milestones; or iii) Proximal weakness; or iv) Weakness in trunk righting/derotation; or v) Hypotonia; or vi) Absence of deep tendon reflexes; or vii) Failure to gain weight appropriate for age; or viii) Any active chronic neurogenic changes; or ix) A compound muscle action potential below normative values for an age-matched child. Defined signs and symptoms of type IIIa SMA are: i) Onset between 18 months and 3 years of age; and ii) Failure to meet or regression in ability to perform age-appropriate motor milestones; or iii) Proximal weakness; or iv) Hypotonia; or v) Absence of deep tendon reflexes; or vi) Failure to gain weight appropriate for age; or vii) Any active chronic neurogenic changes; or viii) A compound muscle action potential below normative values for an age-matched child.
22350	**Prescribing Instructions:** Recognised hospitals in the management of SMA are Lady Cilento 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.
26600 FULL	**Prescribing Instructions:** Application for authorisation of initial treatment must be in writing 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) specification of SMA type (I, II or IIIa); and (ii) sign(s) and symptom(s) that the patient has experienced; and (iii) patient's age at the onset of sign(s) and symptom(s).
26576	**Administrative Advice:** An outcome on the authority application is not immediate, but will follow in due course. Electronic upload is encouraged to reduce processing time.
25744 CAR	**Administrative Advice:** Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos Or mailed to: Services Australia Complex Drugs Reply Paid 9826 HOBART TAS 7001
7606	**Administrative Advice:**No increase in the maximum quantity or number of units may be authorised.
7607	**Administrative Advice:**No increase in the maximum number of repeats may be authorised.

7608	**Administrative Advice:** Special Pricing Arrangements apply.

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
NUSINERSEN					
nusinersen 12mg/5ml injection, 5ml vial	11378W (Pub) 11476B (Priv)	1	1	0	Spinraza

Concept ID (for internal Dept. use)	
	Category / Program: Section 100 – Highly Specialised Drugs Program (Public/Private hospitals code)
	Prescriber type: ☒Medical Practitioners
	Restriction Type ☒Authority Required – immediate/real time assessment by Services Australia
21163	**Indication:** Spinal muscular atrophy (SMA)
Edit	**Treatment Phase:** 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
25333	**Treatment criteria:**
25332	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
	AND
NEW 27612	**Clinical criteria:**
11364 NEW 27611	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 risdiplam for this condition
	AND
27598	**Clinical criteria:**
New CC1 27597	The treatment must not be in combination with PBS-subsidised treatment with risdiplam for this condition
	AND
22077	**Clinical criteria:**
22076	The treatment must be given concomitantly with standard of care for this condition
	AND
22104	**Clinical criteria:**
22103	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
22350	**Prescribing Instructions:** Recognised hospitals in the management of SMA are Lady Cilento 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.
22105	**Prescribing Instructions:** Invasive permanent assisted ventilation means ventilation via tracheostomy tube for greater than or equal to 16 hours per day.
NEW 27613	**Prescribing Instructions:** In a patient who wishes to switch from PBS-subsidised risdiplam to PBS-subsidised nusinersen for this condition a wash out period may be required.
25745 CAR	**Administrative Advice:** Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation

	8 a.m. to 5 p.m. EST Monday to Friday).
7606	**Administrative Advice:** No increase in the maximum quantity or number of units may be authorised.
7607	**Administrative Advice:** No increase in the maximum number of repeats may be authorised.
7608	**Administrative Advice:** Special Pricing Arrangements apply.

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 patients with SMA Types 1, 2 or 3a who are aged 18 years or under at treatment initiation. Roche is working with the Department of Health towards a PBS listing in this patient population at the earliest opportunity.

Roche is disappointed the PBAC did not recommend risdiplam for patients with SMA Type 3b aged 18 years or under at treatment initiation and patients with SMA Types 1, 2 or 3 aged over 18 years at treatment initiation. Roche will evaluate the options available within the parameters of the existing data and collaborate with all stakeholders to find a suitable path forward.

Roche would like to take this opportunity to thank the many members of the SMA community and healthcare professionals who supported the submission.

11 Corrigendum

The following changes were made to the public summary document:

Change made	Date of revision
Paragraph 6.52: typographical error where 'nusinersen' changed to 'risdiplam'	2 July 2021
Paragraph 7.4: Updates to the risdiplam restriction including removing a washout period when stopping treatment with nusinersen; and that eligible patients would be able to swap between treatment with nusinersen and risdiplam without requiring prescribers to resubmit the initial evidence of eligibility.	2 July 2021
Section 8 Recommended Listing: The clinical criterion pertaining to combination therapy has been revised to 'The treatment must not be in combination with PBS-subsidised treatment with nusinersen for this condition'. This change will also be reflected in flow on changes to nusinersen.	2 July 2021