

## 7.03 NUSINERSEN, Solution for injection 12 mg in 5 mL, Spinraza<sup>®</sup>, Biogen Australia Pty Ltd

### 1 Purpose of resubmission

- 1.1 The resubmission requested extension of the current Section 100, Authority Required, Highly Specialised Drugs Program listing for nusinersen to include pre-symptomatic initiation of treatment of nusinersen in patients with genetically confirmed *Survival-of-Motor-Neuron 1 (SMN1)* deletion or mutation and a *Survival-of-Motor-Neuron 2 (SMN2)* gene copy number of 1 or 2 (i.e. *SMN2* copy number  $\leq 2$ ).
- 1.2 Extension of listing was requested on the basis of a cost-effectiveness analysis versus the standard of care (SoC), which was symptomatic treatment with nusinersen. Table 1 provides a summary of the key components of the resubmission.

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

Component	Description
Population	Patients with confirmed genetic diagnosis of SMA ( <i>SMN1</i> deletion or mutation) who have an <i>SMN2</i> copy number of <u>1 or 2</u>
Intervention	Pre-symptomatic initiation of treatment: Nusinersen administered at a dose of 12 mg via intrathecal injection with four loading doses and two maintenance doses in Year 1 and three doses per year thereafter (refer to Section 4.1) after genetic diagnosis
Comparator	Symptomatic initiation of treatment with nusinersen: Nusinersen administered as above, to patients with a diagnosis of SMA and who had the onset of two symptoms prior to 3 years of age (i.e. SMA Type I, II or IIIa) as per the existing PBS listing. Noting that age of onset is a defined "symptom" of SMA.
Outcomes	<ul style="list-style-type: none"> <li>• Time to death or respiratory intervention (Primary endpoint)</li> <li>• Survival and Motor function (assessed by HINE, CHOP INTEND, and WHO instruments)</li> <li>• Safety</li> </ul>
Clinical claim	Pre-symptomatic initiation of treatment with nusinersen is clinically superior in terms of comparative effectiveness and no worse in terms of comparative safety, compared to symptomatic initiation of treatment with nusinersen

Source: Table 1-4, p26 of the resubmission

CHOP-INTEND = Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HINE = Hammersmith Infant Neurological Examination; SMA = spinal muscular atrophy; SMN = survival of motor neuron; WHO = World Health Organization  
Underline indicates difference to the previous submission. In the previous submission, population included patients with *SMN2* copy number of 1, 2 or 3. In the resubmission patients with *SMN2* copy  $\leq 3$  has been included as an 'alternative scenario'.

### 2 Background

#### Registration status

- 2.1 Nusinersen was TGA registered for the treatment of 5q spinal muscular atrophy (SMA) on 2 November 2017. The TGA indication would include pre-symptomatic initiation of treatment in patients with a genetic diagnosis of *SMN1* deletion or mutation.

### Previous PBAC consideration

2.2 A previous submission was first considered at the July 2019 meeting, with a subsequent consideration at the November 2019 meeting following advice from MSAC in August 2019 regarding the prognostic value of *SMN2* copy number, accuracy of the *SMN2* copy number variation testing and additional clinical expert advice.

2.3 The key matters of concern are summarised in Table 2.

**Table 2: Summary of key matters of concern**

Component	Matter of concern (November 2019)	How the resubmission addresses it
PBS restriction	The PBAC considered that in the absence of further information to better predict the progression of pre-symptomatic patients with SMA, it may be appropriate to restrict any future listing of nusinersen for the pre-symptomatic initiation of treatment to those with 2 or less copies of <i>SMN2</i> (para. 11.4).	Proposed listing for base-case scenario restricted to patients with 1 or 2 copies of <i>SMN2</i> . Proposed listing under alternative scenario allows patients with 1, 2 or 3 <i>SMN2</i> copies to receive treatment with nusinersen.
Clinical efficacy	The PBAC considered there was likely an incremental benefit from pre-symptomatic treatment with nusinersen compared with symptomatic treatment. However, the magnitude of incremental benefit could not be ascertained without appropriate comparative data (para. 11.3).	Not addressed.
Economic	The PBAC considered the economic model was unsuitable for decision making based on issues around extrapolation of treatment effect, estimated incremental duration of treatment, estimated utility gain and assumption of no difference in adverse events between pre-symptomatic initiation of treatment and symptomatic treatment (para. 11.6).	Updated analysis provided to address concerns raised around extrapolation of treatment effect, incremental duration of treatment, utility gain and assumption of no difference in adverse events (para 6.23 to 6.42).
Potential rebate for SMA Type II and IIIa	The PBAC noted that the sponsor had not confirmed whether the rebate for ██████████ which currently applies for patients diagnosed with SMA Type II or IIIa is intended to be extended to patients who initiate treatment prior to the onset of symptoms (para. 11.7).	Sponsor did not propose a rebate for ██████████ for patients who initiate treatment pre-symptomatically.
Financial estimate inputs	The PBAC advised that any resubmission should include revised financial estimates to account for underestimate in treatment duration, potential increase in SMA screening and for patients enrolled in any ongoing clinical trials for investigating treatments for pre-symptomatic patients genetically diagnosed with SMA (para. 11.8).	Updated financial estimates include revised treatment duration used in updated economic model, but SMA screening costs and grandfathered patients were not included in the financial estimates (para 6.51 to 6.61.)
Availability of <i>SMN1</i> testing	The PBAC considered that equity of access to newborn screening for SMA remains an issue as newborn screening costs in states and territories apart from NSW and ACT are currently borne by public hospitals and private payers (Para 11.9)	Not addressed.

Source: Table 0-1, p16 of the resubmission  
ES = executive summary

## 3 Requested listing

3.1 The requested listing is provided in Table 3. The resubmission proposed amending the existing listing to include pre-symptomatic initiation of treatment. Underlined text reflects the changes from the previous submission. The only difference between the

restrictions proposed in the resubmission and the previous submission was the change in SMN2 copy number threshold (from  $\geq 3$  to  $\geq 2$ ).

**Table 3: Requested restriction for nusinersen**

Name, restriction, manner of administration, form	Maximum quantity (packs)	No. of repeats	Dispensed price for maximum quantity	Proprietary name and manufacturer
NUSINERSEN Initial treatment 12mg*/5mL injection, 1 x 5 mL vial	1	3	\$110,000 (public)** \$110,007.15 (private)	Spinraza, Biogen Australia Pty Ltd
Continuing treatment 12mg*/5mL injection, 1 x 5 mL vial	1	2	\$█ (effective price) \$110,000 (public)** \$110,007.15 (private) \$█ (effective price)	

<b>Initiation</b>	
Category/Program:	Section 100 – Highly Specialised Drugs Program
PBS indication:	Treatment of <u>pre-symptomatic</u> , infantile-onset and childhood-onset SMA
Treatment phase:	Initial – New patients
Restriction:	Section 100 – Highly Specialised Drugs Program <input checked="" type="checkbox"/> Authority Required - In Writing
Treatment criteria:	Must be treated by a specialist medical practitioner experienced in the diagnosis and management of SMA associated with a neuromuscular clinic of a recognised hospital in the management of SMA; or in consultation with a specialist medical practitioner experienced in the diagnosis and management of SMA associated with a neuromuscular clinic of a recognised hospital in the management of SMA.
Clinical criteria:	The condition must 5q homozygous deletion, mutation of, or compound heterozygous mutation in the <u>SMN1 gene of Type I, II or IIIa</u> ; AND 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 OR Patient must be genetically diagnosed with SMA with a confirmed SMN2 copy number of <u>1 or 2 or 3</u> prior to onset of signs and symptoms; AND The treatment must be given concomitantly with standard of care for this condition. AND The treatment must not exceed four loading doses (at days 0, 14, 28 and 63) under this restriction.
Population criteria:	Patient must be 18 years of age or under.
<b>Grandfathering</b>	
Treatment phase:	Grandfathering
Restriction:	<input checked="" type="checkbox"/> Authority Required - In Writing
Treatment criteria:	Must be treated by a specialist medical practitioner experienced in the diagnosis and management of SMA associated with a neuromuscular clinic of a recognised hospital in the management of SMA; or in consultation with a specialist medical practitioner experienced in the diagnosis and management of SMA associated with a neuromuscular clinic of a recognised hospital in the management of SMA.
Clinical criteria:	Patient must have previously received non-PBS-subsidised treatment for this condition with this drug prior to PBS listing [PBS listing date]; AND The condition must be 5q homozygous deletion, mutation of, or compound heterozygous mutation in the <u>SMN1 gene</u> ; AND 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 OR Patient must be genetically diagnosed with SMA with a confirmed SMN2 copy number of 1 or 2 prior to onset of signs and symptoms; AND The treatment must be given concomitantly with standard of care for this condition. AND

	The treatment must not exceed four loading doses (at days 0, 14, 28 and 63) under this restriction.
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Underlined text reflects the change from the previous submission

Source: Table 1-7, p38 and 1-10, p40 of the resubmission.

- 3.2 The resubmission stated that the continuation criteria for the current PBS restriction for nusinersen would also be applicable under the proposed initiation restriction, therefore no specific continuation criteria was proposed.
- 3.3 An effective price of \$ [REDACTED] per dose was proposed. This was the same as the previous submission and the current listing.
- 3.4 The requested maximum quantity and number of repeats remain unchanged from the previous submission. The number of repeats requested for continuing treatment (two) is greater than the number of repeats for the current continuing treatment listing (zero). The PBAC considered that an increase in repeats compared to the current listing was not adequately justified.
- 3.5 The ESC previously (paragraph 2.3, nusinersen, Public Summary Document (PSD), July 2019) considered that it would be appropriate to limit pre-symptomatic initiation of treatment to patients less than three years of age, and noted that this was supported in the Pre-Sub-Committee Response (PSCR). However, the requested restriction in the resubmission only restricts initiation to patients less than 18 years of age. The PBAC noted that a separate restriction would be required to limit pre-symptomatic initiation of treatment to patients less than three years of age as the current restriction specifies an age limit of 18 years of age.
- 3.6 A request for a grandfathering restriction is new to the resubmission. The resubmission noted that, as of 26 February 2020, there were three pre-symptomatic patients in Australia currently treated with nusinersen who would be expected to be grandfathered onto the PBS. The pre-PBAC Response stated there is currently only one patient receiving nusinersen free of charge and this patient would not be eligible for grandfather treatment as they have an SMN2 copy number >2. The PBAC noted that a grandfather restriction may not be required.

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

## 4 Population and disease

- 4.1 Spinal muscular atrophy is an autosomal recessive progressive neuromuscular disease caused by mutations or deletions in the *SMN1* gene on chromosome 5q. Alterations to this gene results in deficiency of SMN protein, which in turn results in loss of motor function and respiratory failure, which is a major cause of morbidity and mortality. The *SMN2* gene also produces SMN protein, albeit at low levels which are not sufficient to sustain survival of spinal motor neuron function. As *SMN2* copy number varies from patient to patient, there is a clinical spectrum of the disease where fewer *SMN2* gene copies sometimes correlate to earlier age of onset and increased disease severity SMA is classified based on age of onset and maximal motor function achieved,

into types (0, I, II, III and IV) with type III SMA further classified into subtypes (a, b, c), see Table 4.

**Table 4: Classification of SMA based on age of onset and maximal motor function achieved**

Classification	SMA type	Age at symptom onset	Maximal motor milestone	Likely/Common SMN2 copy numbers	Motor ability and additional features	Prognosis <sup>^</sup>
Pre-natal	0	Pre-natal (before birth)	None	<b>1</b>	Severe hypotonia; Unable to sit or roll*	Death within weeks
Infantile-onset	I	<6 months	None	<b>1, 2, 3</b>	Severe hypotonia; Unable to sit or roll <sup>#</sup>	Death by 2 years
Childhood-onset	II	6 - 18 months	Sitting	<b>2, 3, 4</b>	Proximal weakness; Unable to walk independently	Survival into adulthood
	III	<3 years (IIIa) >3 years (IIIb) >12 to ≤18 years (IIIc)	Walking	<b>3, 4, 5</b>	May lose ability to walk	Normal lifespan
Adult-onset	IV	>18 years	Normal	<b>4, 5, 6</b>	Mild motor impairment	Normal lifespan

Abbreviations: SMA, spinal muscular atrophy; SMN; survival-of-motor-neuron 2 gene

\* Need for respiratory support at birth; contractures at birth, reduced fetal movements.

<sup>^</sup> Prognosis varies with phenotype and standard of care interventions

<sup>#</sup> Ia joint contractures present at birth; Ic may achieve head control.

Note: The most common number of copies of the SMN2 gene for each type of SMA are bolded.

Source: Table 1-3, p25 of the resubmission

4.2 The resubmission noted that advice from MSAC was that “SMN2 copy number variation offers some prognostic value and that MSAC considered the prognostic value was more reliable for infants with two or less copies of SMN2 compared with three or less copies of SMN2. The PBAC noted that although MSAC considered SMN2 copy number to be the main source of prognostic information for SMA severity, MSAC advised there are several other genetic components besides the SMN2 copy number that may also modify the phenotype to some extent” (paragraph 11.2, nusinersen, Addendum to the July 2019 PSD, November 2019). As a result, MSAC advised the inclusion of additional criteria for pre-symptomatic patients with three copies of SMN2 in the event that such patients were also considered to be eligible for nusinersen (paragraph 10.3, nusinersen, Addendum to the July 2019 PSD, November 2019).

4.3 Under the proposed restriction, patients with confirmed SMN1 deletion or mutation and an SMN2 copy number ≤2 will be treated with nusinersen in the absence of any SMA symptoms. Currently, nusinersen is only PBS subsidised for patients who experienced at least two of the defined signs and symptoms of SMA Type I, II or IIIa prior to 3 years of age.

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

## 5 Comparator

- 5.1 The resubmission nominated SoC (i.e. symptomatic treatment with nusinersen upon diagnosis of SMA Types I, II or IIIa and identification of two signs or symptoms of SMA, noting that age of onset is described as a ‘sign or symptom’ in the current listing) as the main comparator. The nominated comparator was previously considered appropriate and has been accepted by the PBAC.

## 6 Consideration of the evidence

- 6.1 The clinical evidence presented in the resubmission was unchanged from the previous submission, with the exception of inclusion of an updated periodic safety report for the period of 31 May 2019 to 30 November 2019 from the NURTURE trial. For brevity, only a summary of the clinical evidence as considered by the PBAC (July 2019 and November 2019) and MSAC (August 2019) have been provided.

### ***Sponsor hearing***

- 6.2 There was no hearing for this item.

### ***Consumer comments***

- 6.3 The PBAC noted and welcomed the input from individuals (11), health care professionals (5) and organisations (4) via the Consumer Comments facility on the PBS website. The comments emphasised the importance of early diagnosis and treatment of SMA. The comments from health care professionals noted the improvement in outcomes of patients treated early.
- 6.4 The Genetic Undiagnosed and Rare Disease (GUARD) Collaboration, Spinal Muscular Atrophy Australia, Rare Voices Australia and the National Paediatric Medicines Forum supported extension of the current listing to include pre-symptomatic initiation of treatment. The organisations noted the rapidly changing therapeutic landscape for SMA and highlighted that the current requirement for symptoms to develop prior to accessing subsidised treatment has a considerable psychological impact on families.

### ***Prognostic value of SMN2 copy number***

- 6.5 The prognostic value of *SMN2* copy number in SMA was considered by MSAC as part of the co-dependent technology submission in July 2019 at its August 2019 meeting (Application no. 1589). MSAC noted that:
- The most relevant data come from studies which reported SMA Type IIIa and IIIb separately.
  - *SMN2* copy number variation does offer some prognostic value – that is, more copies of *SMN2* generally results in less severe SMA, and less copies of *SMN2* generally results in more severe SMA. MSAC considered that the prognostic value was more reliable for infants with  $\leq 2$  copies of *SMN2* compared with  $\leq 3$  copies. However, this correlation between *SMN2* copy number and disease severity appears to be imperfect.

- Patients with pre-symptomatic SMA and one or two copies of *SMN2* could be considered suitable as a prerequisite part of the eligibility criteria for any extended PBS restriction for nusinersen (Table 5). However, MSAC also advised that patients with pre-symptomatic SMA and three copies of *SMN2* should also undergo clinical assessment and electromyography testing by a neuromuscular specialist to detect any early signs of motor abnormality as a prerequisite part of the eligibility criteria for any extended PBS restriction for nusinersen. The purpose of this would be to reduce some of the negative consequences of the false positive rate estimated above at 4.28% (Sum of *SMN2* copy number 1, 2 or 3 and Type IIIa or IV) based on *SMN2* copy number alone (Table 6).
- That there is insufficient evidence on the prevalence of patients who are genotypically abnormal but remain phenotypically normal throughout their life to modify the estimated proportions of pre-symptomatic patients being eligible for nusinersen based on *SMN2* copy number and associated false positive rates.

**Table 5: Proportion of SMA patients eligible for nusinersen with pre-symptomatic initiation of treatment and in current practice based on *SMN2* copy number threshold of 2 or less, using studies which only reported different SMA types including IIIa and IIIb**

		Current practice		
		Eligible	Not eligible	All
Pre-symptomatic initiation of treatment	Eligible	27.45% (True positives)	0.56% (False positives)	28.01%
	Not eligible	57.03% (False negatives)	14.96% (True negatives)	71.99%
	All	84.48%	15.52%	100.00%

Source: August 2019 MSAC Public Summary Document for Application 1589.  
Abbreviations: SMA = Spinal Muscular Atrophy, SMN = survival of motor neuron

**Table 6: Proportion of SMA patients eligible for nusinersen with pre-symptomatic initiation of treatment and in current practice based on *SMN2* copy number threshold of 3 or less, using studies which only reported different SMA types including IIIa and IIIb**

		Current practice		
		Eligible	Not eligible	All
Pre-symptomatic initiation of treatment	Eligible	76.72% (True positives)	4.28% (False positives)	80.99%
	Not eligible	7.76% (False negatives)	11.25% (True negatives)	19.01%
	All	84.48%	15.52%	100.00%

Source: August 2019 MSAC Public Summary Document for Application 1589.  
Abbreviations: SMA = Spinal Muscular Atrophy, SMN = survival of motor neuron

6.6 The resubmission appropriately used the revised estimates of distribution of SMA type by copy number, based only on publications which reported across multiple SMA types (as assessed by MSAC) including Type IIIa and IIIb, to inform the distribution of SMA type by *SMN2* copy number in the economic model and financial estimates (see Table 7). The ESC considered that these revised estimates are more likely to reflect the distribution of SMA type and *SMN2* copy number of the eligible population compared to the distribution presented in the July 2019 submission, which was informed in part by studies that did not report across the full spectrum of SMA. However, the ESC noted there would always be some uncertainty around the SMA type of patients that would

be treated as there would be no way to confirm this in the patient population following pre-symptomatic initiation of treatment.

**Table 7: Distribution of SMA type and SMN2 copy numbers considered by MSAC August 2019 and applied in the economic model and financial estimates in current resubmission**

SMN2 copy number	SMA Type					All
	I	II	IIIa	IIIb	IV	
1	1.69%	0.11%	0.00%	0.00%	0.00%	1.80%
2	23.40%	2.02%	0.22%	0.56%	0.00%	26.21%
3	8.89%	30.26%	10.12%	3.71%	0.00%	52.98%
4	0.11%	2.14%	5.51%	10.01%	0.67%	18.45%
5+	0.00%	0.00%	0.00%	0.56%	0.00%	0.56%
All	34.08%	34.53%	15.86%	14.85%	0.67%	100.00%
SMN2 ≤2 <sup>a</sup>	89.56%	7.63%	0.80%	2.01%	0.00%	100.00%
SMN2 ≤3 <sup>b</sup>	41.94%	40.00%	12.78%	5.28%	0.00%	100.00%

Source: Table 3-4, p 146 of the resubmission, Nusinersen Economic Model\_March2020.xlsx

Key: Green, proportion of patients who would be eligible for nusinersen with or without pre-symptomatic testing (true positives). Orange, proportion of patients eligible based on pre-symptomatic testing but not in current practice (false positives). Yellow, proportion of patients eligible based on current PBS listing only (false negatives). Red, proportion of patients who would not be eligible based on either listing (true negatives)

Expressed as a percentage of all patients (N=901). Studies included were Amara 2012, Arkblad 2009, Kaneko 2017, Jedrzejowska 2009, Medrano 2016, Petit 2011, Scarciolla 2006, Tiziano 2010, Tran 2008, Wadman 2017

<sup>a</sup> The distribution presented represents the proportion of patients with each SMA type among all patients with an SMN2 copy number ≤2.

<sup>b</sup> The distribution presented represents the proportion of patients with each SMA type among all patients with an SMN2 copy number ≤3

### **Accuracy and performance of proposed test for determination of SMN2 copy number**

6.7 The accuracy and performance of the laboratory tests to determine SMN2 copy number was also considered by MSAC as part of the co-dependent technology submission in July 2019 at its August 2019 meeting. MSAC considered that both quantitative polymerase chain reaction (qPCR) and multiplex ligation-dependent probe amplification (MLPA) had a high degree of accuracy at determining SMN2 copy number. However, none of the studies on the accuracy and performance of these tests were conducted prospectively among patients with confirmed SMN1 deletion/mutation where copy numbers were to be determined, which is the proposed use of the tests.

### **Clinical evidence of pre-symptomatic initiation of treatment with nusinersen**

6.8 As per the previous submission, the clinical efficacy of pre-symptomatic initiation of treatment with nusinersen in the resubmission was based on an interim analysis (dated 15 May 2018) of an ongoing phase 2, non-randomised, non-controlled, open-label single arm study of nusinersen in 25 pre-symptomatic infants with confirmed homozygous or compound heterozygous mutation in the SMN1, and either 2 (n=15) or 3 (n=10) copies of SMN2: the NURTURE study. NURTURE was considered to have a high risk of bias as it was an open label single arm study. The PBAC has previously

noted that as NURTURE did not provide appropriate comparative data, incremental benefit of pre-symptomatic initiation of treatment versus symptomatic treatment could not be determined from NURTURE alone (paragraph 7.4, nusinersen, Addendum to the July 2019 PSD, November 2019).

- 6.9 A naïve informal indirect comparison of the NURTURE study with data derived from ENDEAR and CS3A studies (and the extension study SHINE) for infantile-onset and from the CHERISH study for childhood onset SMA, was also presented with the aim of providing some clinical context to the findings of the NURTURE study. This comparison was previously presented in the July 2019 submission. The PBAC previously noted that there were transitivity issues associated with the comparison and that the reliability of the comparison was limited (paragraph 7.4, nusinersen, Addendum to the July 2019 PSD, November 2019).
- 6.10 Details of the studies presented in the resubmission are provided in Table 8.

**Table 8: Studies and associated reports presented in the resubmission**

Study ID	Protocol title/ Publication title	Publication citation
<b>Non-randomised study forming the primary evidence</b>		
SM291/ NURTURE	<p>A Study of Multiple Doses of Nusinersen (ISIS 396443) Delivered to Infants With Genetically Diagnosed and Pre-symptomatic Spinal Muscular Atrophy [NCT02386553]</p> <p><i>De Vivo DC, Bertini E, Swoboda KJ, Hwu WL, et al. Nusinersen initiated in infants during the presymptomatic stage of spinal muscular atrophy: Interim efficacy and safety results from the Phase 2 NURTURE study</i></p> <p>Interim Clinical Study Report</p> <p>Interim Clinical Study Report</p> <p>Bertini E, Hwu WL, Reyna SP, Farwell W, Gheuens S, Sun P, et al. Efficacy and safety of nusinersen in infants with presymptomatic spinal muscular atrophy (SMA): Interim results from the NURTURE study.</p> <p>46th Annual Meeting of the Child Neurology Society.</p> <p>Crawford T, De Vivo D, Bertini E, Hwu WL, Foster R, Bhan I, et al. Nusinersen in infants who initiate treatment in a presymptomatic stage of spinal muscular atrophy (SMA): Interim efficacy and safety results from the phase 2 nurture study.</p> <p>De Vivo D, Bertini E, Hwu WL, Foster R, Gheuens S, Farwell W, et al. One-year outcomes following treatment with nusinersen: Interim results from the NURTURE study of presymptomatic infants with genetically diagnosed spinal muscular atrophy (SMA).</p> <p>De Vivo DC, Bertini E, Hwu W, Foster R, Bhan I, Gheuens S, et al. Nusinersen in infants who initiate treatment in a presymptomatic stage of spinal muscular atrophy (SMA): Interim results from the Phase 2 NURTURE study.</p> <p>De Vivo DC, Hwu WL, Reyna SP, Farwell W, Gheuens S, Sun P, et al. Interim efficacy and safety results from the Phase 2 NURTURE study evaluating nusinersen in presymptomatic infants with spinal muscular atrophy.</p> <p>Mercuri E, Finkel RS, Farrar M, Richman S, Foster R, Hughes S, et al. Infants and children with spinal muscular atrophy (sma) treated with nusinersen in clinical trials: An integrated safety analysis.</p> <p>Nct. A Study of Multiple Doses of Nusinersen (ISIS 396443) Delivered to Infants With Genetically Diagnosed and Presymptomatic Spinal Muscular Atrophy.</p>	<p><i>Neuromuscular Disorders</i> 2019; 29(842-56)</p> <p>May 2018</p> <p>February 2017</p> <p>European Journal of Paediatric Neurology. 2017;21:e14</p> <p>Annals of Neurology. 2017;82</p> <p>Annals of Neurology. 2018;84:S392</p> <p>Annals of Neurology. 2017;82:S265-S6</p> <p>Canadian Journal of Neurological Sciences. 2018;45:S12-S3</p> <p>Neurology. 2017;88(16)</p> <p>Developmental Medicine and Child Neurology. 2017;59:16-7</p> <p><a href="https://clinicaltrials.gov/show/nct02386553">https://clinicaltrials.gov/show/nct02386553</a>. 2015</p>
<b>Supplementary studies used for the informal indirect comparison</b>		
CS3B/ ENDEAR	A Study to Assess the Efficacy and Safety of Nusinersen (ISIS 396443) in Infants With Spinal Muscular Atrophy [NCT02193074]	10 February 2017
CS4/ CHERISH	A Study to Assess the Efficacy and Safety of Nusinersen (ISIS 396443) in Participants With Later-onset Spinal Muscular Atrophy (SMA) [NCT02292537]	6 June 2017
CS3A	<p>A Study to Assess the Efficacy, Safety and Pharmacokinetics of Nusinersen (ISIS 396443) in Infants With Spinal Muscular Atrophy (SMA) [NCT01839656]</p> <p>Finkel et al. Treatment of infantile-onset spinal muscular atrophy with nusinersen: a phase 2, open-label, dose escalation study.</p>	<p>21 August 2016</p> <p>The Lancet 2016. 388 (10063): 3017-3026</p>

Study ID	Protocol title/ Publication title	Publication citation
	Finkel et al. Interim results of a phase 2 clinical study of nusinersen (ISIS-SMNRX) in patients with infantile-onset spinal muscular atrophy.	Annual of Neurology 2016. 80; S371-372
	Finkel et al. Interim results of a phase 2 clinical study of nusinersen (ISIS-SMNRX) in patients with infantile-onset spinal muscular atrophy.	Neurology 2016. 86 (16); Supplement P5.004
	Finkel et al. Results of a phase 2 open-label study of ISIS-SMNRx in patients with infantile (type 1) spinal muscular atrophy.	Neurology 2014. 82 (10); Supplement S6.003
	Finkel et al. Results of a phase 2 open-label study of ISIS-SMNRx in patients with infantile (Type 1) spinal muscular atrophy.	Neuromuscular disorders 2014. 24 (9-10); 920

Source: Table 2d.-2-27,p92 of the resubmission and Table 2.2.3, p48-49 of the November 2017 PBAC submission.

6.11 The key features of the included studies are summarised in Table 9. As in the previous submission, none of the results from any of the identified studies were used in the economic evaluation.

**Table 9: Key features of the included evidence**

Study	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
NURTURE	25	OL, NC, 5 years Interim analysis 27.14 months	High*	Age <6 weeks with SMA and no symptoms: 2 or 3 SMN2 copies	EFS, OS, Motor milestones, CHOP Intend	Not used
ENDEAR	121	R, DB, MC 13 months	Low	Infantile-onset SMA (Type I)	EFS, OS, HINE (Section 2)	
CHERISH	126	R, DB, MC 16 months	Low	Childhood-onset SMA (Type II)	HFMSE	
CS3A	20	OL, MC, NC, multi-dose 3.7 years	High*	Infantile-onset SMA (Type I)	Motor milestones	
SHINE	142 Type I SMA and 182 Type II SMA patients	OL, extension trial 5 years total from enrolment in first trial	High*	Type I and Type II SMA patients from the ENDEAR, CHERISH, CS3A or CS12 trials	EFS, OS, HINE (Section 2), CHOP Intend, Motor milestones, HFMSE, quality of life	

Abbreviations: O, open label; OS, overall survival; EFS, event-free survival; NC, non-comparative; R, randomised; DB, double-blind; MC, multi-centre; SMA, spinal muscular atrophy; HINE, Hammersmith Infant Neurological Examination; HFMSE, Hammersmith Functional Motor Scale-Expanded; CHOP INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders

\* Considered to be high risk of bias being open-label and non-comparative studies.

Source: Table 6, p9 nusinersen PSD November 2019

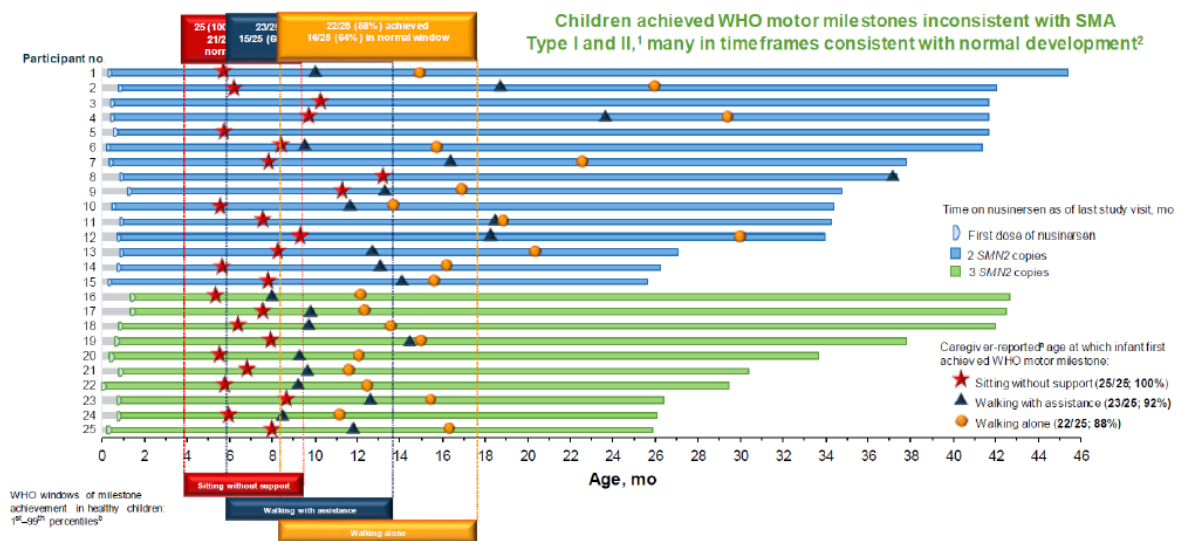
### Comparative effectiveness

6.12 The data from interim-analysis (15 May 2018) on the efficacy of pre-symptomatic initiation of treatment with nusinersen in SMA patients for the outcome of SMA symptom onset by SMN2 copy number can be summarised as:

- SMN2 copy number = 1: no data. Unknown efficacy or benefit. The resubmission claimed that this represents only a small proportion of patients (3%) and it is likely these patients would be symptomatic at birth or become symptomatic shortly after and be able to be treated under the current PBS restriction.

- *SMN2* copy number = 2: 10/15 (67%) patients in NURTURE developed SMA symptoms by 13 months of age and 7/11 (64%) of patients who reached 24 months of age at the end of interim follow-up developed SMA symptoms by this age. The longer-term course of disease and outcomes are unknown. The ESC (paragraph 6.10, nusinersen, PSD, July 2019) noted these results did not support a clear effect on symptom onset with pre-symptomatic initiation of treatment for patients with an *SMN2* copy number of 2. Many patients with an *SMN2* copy number of 2 would experience symptom onset prior to 6 months of age, but others could have a later onset of symptoms.
  - *SMN2* copy number = 3: 2/10 (20%) patients in NURTURE developed SMA symptoms by 13 months of age, but 0/5 of patients who reached 24 months of age at the end of interim follow-up developed SMA. However, it is plausible that the follow-up period was insufficient for symptom onset to be observed in the study. The ESC (paragraph 6.10, nusinersen, PSD, July 2019) considered the extent to which symptom onset was delayed for patients with an *SMN2* copy number of 3, if any, was uncertain as patients with an *SMN2* copy number of 3 may develop symptoms after 24 months of age.
- 6.13 At the updated interim analysis time point (median follow up 33.8 months), no patients enrolled in NURTURE had died, and four patients with 2 *SMN2* copies met the primary endpoint of death or respiratory intervention, with the respiratory intervention having been initiated temporarily for acute, reversible infections. No patient required permanent ventilation. De Vivo et al 2019 provided further detail on the respiratory support required. Two patients who no longer required respiratory support at the interim cut-off had received respiratory intervention for  $\geq 6$  hours per day for totals of 20 and 266 days during the course of NURTURE. Two patients who remained on respiratory support at the interim cut off continued to receive respiratory intervention for two and ten hours per day, respectively, and had received respiratory intervention for  $\geq 6$  hours per day for totals of 236 days and 644 days, respectively, over the course of the study.
- 6.14 At the updated interim analysis time point (33.8 months), all except one patient with 3 copies of *SMN2* achieved the WHO motor milestones in the expected timeframe for normal healthy infants. However 9/15 (60%) of patients with 2 copies of *SMN2* failed to meet the expected WHO milestones at around 14 months of age. The majority of patients with 2 copies of *SMN2* had significant delays in reaching HINE milestones for the majority of patients (Figure 1).

Figure 1: Achievement of WHO motor milestones based on caregiver observation with confirmation by site at subsequent visit – ITT set at 33.8 months



Source: Figure 3, para 6.20 p14 of nusinersen, Addendum to the July 2019 PSD, November 2019

Note: the red, blue and yellow shaded bars at the base of the figure representing the expected timeframe for achievement of these milestones in normal healthy infants

6.15 The naïve indirect comparison between NURTURE and ENDEAR, CS3A, SHINE and CHERISH was considered inappropriate by the ESC as:

- NURTURE enrolled patients with *SMN2* copy numbers of 2 and 3 whereas ENDEAR enrolled only patients with an *SMN2* copy number of 2 with the most severe form of disease (Type I SMA). Patients enrolled in ENDEAR were likely to have worse outcomes than those enrolled in NURTURE, which was reflected in the mortality rate (13/80, 16%) in nusinersen treated patients in ENDEAR compared to NURTURE in which no deaths were observed; and
- The mean age of patients in CHERISH at screening (3.8 years) was older than the oldest patient enrolled in NURTURE at interim cut-off (847 days, or 2.3 years), indicating that the patients enrolled in CHERISH and NURTURE were at completely different developmental stages (paragraph 6.18, nusinersen, PSD, July 2019).

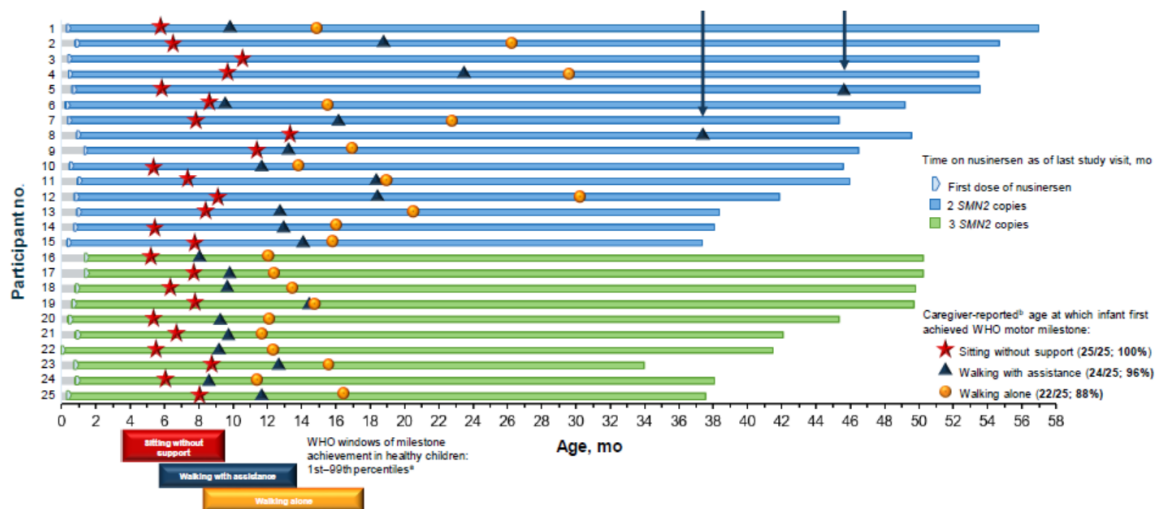
6.16 The PBAC previously considered that key differences between characteristics of the patients enrolled in the ENDEAR, CHERISH and NURTURE trials noted by the ESC meant that a comparison of outcomes from these trials could not reliably inform the magnitude of any incremental benefit (paragraph 7.4, nusinersen, PSD, July 2019)

6.17 Nonetheless, at the November 2019 PBAC meeting, based on the advice from clinicians and the overall available evidence, the PBAC considered there was likely an incremental benefit from pre-symptomatic initiation of treatment with nusinersen compared with symptomatic treatment however, maintained that the magnitude of incremental benefit could not be ascertained without appropriate comparative data. No new data or analysis was presented in the resubmission to address this, and this remains an outstanding issue. The ESC noted that the uncertainty around the magnitude of incremental benefit from pre-symptomatic initiation of treatment

compared with symptomatic treatment remains an outstanding issue in the absence of any new clinical data.

- 6.18 Clinicians experienced in the treatment of SMA considered that patients with severe forms of SMA would derive the most benefit from nusinersen if initiated prior to development of irreversible motor neuron loss, noting that newborns treated at 1 week compared to 6 weeks in NURTURE had better outcomes (paragraph 10.8, nusinersen, Addendum to the July 2019 PSD, November 2019). This could not be verified during the evaluation, as no comparisons between the subgroups depending on age at first dose were reported. Conversely, MSAC ESC (Application no.1589 MSAC PSD, August 2019) noted that in the NURTURE study, early data suggest that patients with 3 copy numbers (and less likely to have severe SMA) are the ones who may be benefitting from early access to treatment. MSAC (Application no.1589 MSAC PSD, August 2019) consider this biologically plausible as nusinersen achieves its pharmacological effect by increasing the function of existing *SMN2* genes.
- 6.19 The pre-PBAC Response reported data from the February 2020 interim analysis with a median follow-up of 45.6 months (Figure 2). The pre-PBAC Response noted the data showed that at the follow-up time point, all patients were alive and no patients have required permanent ventilation or had loss of major motor milestones.

Figure 2: Achievement of WHO motor milestones based on caregiver observation with confirmation by site at subsequent visit – ITT set at 45.6 months



Source: Figure 2, p3 of the pre-PBAC Response

Note: the red, blue and yellow shaded bars at the base of the figure representing the expected timeframe for achievement of these milestones in normal healthy infants

### **Comparative harms**

- 6.20 As there were no comparative studies identified, no comparative harms were noted. The PBAC (paragraph 11.4, nusinersen, Addendum to the July 2019 PSD, November 2019) considered that there may be long-term implications from repeated lumbar puncture administrations, particularly in patients who may not have had nusinersen otherwise (i.e. Type IIIb and Type IV patients). The ESC noted that the resubmission had not addressed concerns around the prospect of overtreatment with nusinersen in patients who would have developed Type IIIb or Type IV SMA and the associated long-term safety of nusinersen in these patients.
- 6.21 All 25 (100%) of patients in NURTURE experienced an adverse event. A total of nine patients (36%) experienced at least one serious adverse event, six of which were considered related to study treatment by the Investigator. The most frequently reported serious adverse events were pneumonia in four patients, respiratory syncytial virus bronchiolitis in two patients, and respiratory distress in two patients. Six adverse events, with one being serious (due to failed lumbar puncture procedure on Day 4) was related to post-lumbar puncture syndrome.
- 6.22 A periodic safety report covering 31 May 2019 to 30 Nov 2019 was presented in the resubmission. No new, ongoing or closed signals were reported in the periodic safety report. The ESC considered that in the absence of long-term safety data to adequately discern any long-term effects of repeated lumbar puncture administrations in infants, the safety of lifetime treatment with nusinersen in this population remains unknown.
- 6.23 The pre-PBAC Response stated that no new safety concerns were identified and all patients have remained on treatment at the recent February 2020 interim analysis time point. The pre-PBAC Response noted there was approximately 7 years of follow-up data across the nusinersen clinical trial program and that based on this data, long-term repeated lumbar puncture administrations are well tolerated.

### **Benefits/harms**

- 6.24 The naïve indirect comparison presented in the resubmission did not allow for a quantitative comparison of the benefits and harms of pre-symptomatic initiation of treatment with nusinersen and SoC. Accordingly, a benefits/harms table has not been presented.

### **Clinical claim**

- 6.25 The resubmission described pre-symptomatic initiation of treatment with nusinersen in patients with genetically diagnosed SMA as superior in terms of effectiveness compared with SoC (symptomatic initiation of treatment) and no worse in terms of comparative safety. The clinical claim was not adequately supported by the evidence presented in the resubmission.
- 6.26 The PBAC previously considered there was likely an incremental benefit from pre-symptomatic initiation of treatment with nusinersen compared with symptomatic

treatment however, maintained that the magnitude of incremental benefit could not be ascertained without appropriate comparative data (paragraph 11.3, nusinersen, Addendum to the July 2019 PSD, November 2019).

- 6.27 The PBAC previously (paragraph 11.4, nusinersen, Addendum to the July 2019 PSD, November 2019) considered that there may be long-term implications from repeated lumbar puncture administrations, particularly in patients who may not have had nusinersen otherwise (i.e. Type IIIb and Type IV patients). The ESC considered the claim of no worse in terms of safety compared to SoC was not adequately supported noting there was a lack of long-term safety data and safety of repeated lumbar puncture in patients who would have developed Type IIIb and Type IV had not been addressed.
- 6.28 The PBAC maintained that the magnitude of clinical benefit was uncertain as no comparative data is available. The PBAC noted that the long-term safety of repeated lumbar puncture in the context of a lifelong disease remains unknown.

### **Economic analysis**

- 6.29 The resubmission presented a cost-utility analysis. The model in the resubmission has significantly changed from that of the previous submission (Table 10) which was considered by PBAC to be unsuitable for decision making (paragraph 11.6, nusinersen, Addendum to the July 2019 PSD, November 2019). However the ESC noted that similar to the previous submission, no data from any of the identified studies was used in the economic evaluation.

**Table 10: Summary of model structure, key inputs and rationale in current resubmission and previous submission**

<b>Component</b>	<b>Current resubmission</b>	<b>Previous submission</b>	<b>Comment</b>
Treatments	Pre-symptomatic initiation of treatment with nusinersen versus Standard of care /symptomatic initiation		Appropriate
Time horizon	20 years in model vs median 2.8 years (33.8 months) in NURTURE	80 years in the model vs 27.1 months in NURTURE	Still likely to be optimistic, given that estimated life expectancy in Type I SMA (which forms 89% of the estimated cohort) is only two years (Table 4).
Outcomes	Quality adjusted life years (QALY)		Reasonable
Method to generate results	Cohort based (Markov) state transition model	Cohort expected value	Reasonable
Health states	13 health states in total: Assume that all patients in model will develop SMA Type I, Type II, Type IIIa or Type IIIb/IV. Within each type, patients may be i) asymptomatic and treated; ii) asymptomatic and untreated; or iii) symptomatic and treated. This results in a total of 12 health states plus death as an absorbing health state.	None	Only 9 health states are actually in the resubmission's model as it was not possible for patients to be in the 'asymptomatic and untreated' state in the pre-symptomatic initiation arm or for patients to be in the 'asymptomatic and treated' state in the SoC arm. May not be reasonable to exclude 'untreated and symptomatic' as a health state in SoC, given that there is often a delay between symptom onset and diagnosis/treatment.

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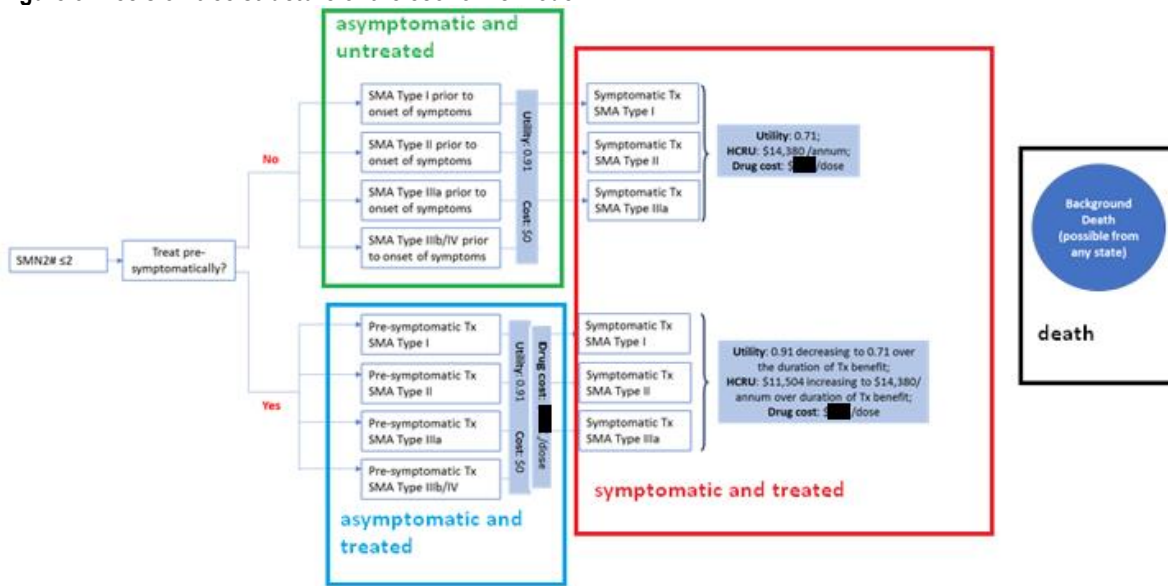
Component	Current resubmission	Previous submission	Comment
Cycle length	6 months	Not applicable	Six monthly cycles may be too long and not sensitive enough to capture the likely rapid progression and deterioration of Type I SMA, which forms 89% of the estimated cohort. Cycle length is reasonably consistent with the dosing frequency of nusinersen (4 months).
Transition probabilities	Time to transition from asymptomatic to symptomatic was assumed to be fixed. No probabilities were applied. Background mortality taken from ABS life tables only.	Not applicable	Possibly unrealistic to have all patients of the same type being symptomatic at the same time. This does not model the degenerative and progressive nature of SMA in the model.
Mortality	As per ABS life tables only. No mortality due to SMA.	0% until 80 years old then all patients die.	Inappropriate to not include disease related mortality for SMA, particularly for Type I SMA.
Utilities	Asymptomatic, untreated = 0.91 Asymptomatic, treated = 0.91 in Year 1 of treatment, decreasing by 0.01 each year to 0.71 after 20 years of treatment Symptomatic, treated = 0.71 (only applicable to standard of care arm)	Pre-symptomatic initiation = 0.91 Symptomatic treatment = 0.71 Maintained over 80 year time horizon	More conservative in resubmission but still based on assumption and possibly optimistic. The resubmission (Figure 3-4, p163) argued that 'a utility gain of 0.1 or more for pre-symptomatic treatment is considered reasonable' based on the naïve indirect comparison of NURTURE and ENDEAR/SHINE, but a more optimistic benefit of 0.2 was applied in the base case of the model. Assumption of incremental utility gain is key driver of the model (Table 11, Table 13)
Other health care costs	Standard of care arm: \$7,190 per cycle when symptomatic Asymptomatic treatment arm: \$5,752 (assumed 20% reduction from standard of care arm) for first cycle after becoming symptomatic, increasing by \$36 each cycle until \$7,190	Pre-symptomatic initiation: \$4,380 healthcare related and \$14,944 non-health care savings per annum	More conservative in resubmission, but still based on assumption. Has only minor/moderate impact on ICER (Table 13 and Table 15)
Proportion of each SMA type in cohort	Type I: 89.56% Type II: 7.63% Type III: 0.80% Type IV: 2.01%	Type I: 52.07% Type II: 28.65% Type III: 13.75% Type IV: 5.54%	Differences were due to (i) the change in SMN2 threshold from $\geq 3$ to $\geq 2$ and (ii) using SMN2 distribution by SMA type from studies which reported the whole spectrum of SMA types only including Type IIIa and IIIb (see Para 6.3).

Source: Table 3-2, p140 of the resubmission, Table 9, p16 nusinersen PSD November 2019

ES = executive summary, SMA = spinal muscular atrophy, SMN = survival of motor neurone, ICER = incremental cost effectiveness ratio, ABS = Australian Bureau of Statistics

6.30 A diagram of the model presented in the resubmission is presented in Figure 3.

Figure 3: Decision tree structure of the economic model



Source: Adapted from Figure 3-1, p143 of the resubmission

6.31 Patients start the model at age 0. All patients in each arm are assumed to have an underlying SMA type and will develop symptoms at a fixed age/cycle, depending on the SMA type. The distribution of patients with each SMA type and the assumed age of onset is summarised in Table 11. It may not be realistic to assume all patients with the same SMA type will be symptomatic at the same time. The ESC considered this assumption was inconsistent with the progression of SMA across the full clinical spectrum of the disease.

Table 11: Proportion of each SMA type and onset of symptoms in model

SMA type	Type I	Type II	Type IIIa	Type IIIb/IV
Proportion <sup>a</sup>	89.56%	7.63%	0.8%	2.01%
Assumed age of symptom onset	6 months (Cycle 2)	12 months (Cycle 3)	2.5 years (Cycle 6)	Assumed to never be symptomatic as will not be treated with nusinersen under current listing
Start treatment in Standard of Care arm	6 months (Cycle 2)	12 months (Cycle 3)	2.5 years (Cycle 6)	Never
Assumed additional treatment period in pre-symptomatic initiation treatment arm	6 months (1 cycle)	12 months (2 cycles)	2.5 years (5 cycles)	20 years (40 cycles)

<sup>a</sup> based on estimated prevalence of each SMA type with SMN2 copy number of 1 or 2 (see Table 2.3 and 3.3.1 of the commentary)

Source: Table 3-3, p144 of the resubmission

6.32 All patients in the SoC arm start in the ‘asymptomatic and untreated’ health state during which they accrue no costs and have an asymptomatic utility of 0.91 (same as the previous submission). Once they reach the corresponding age/cycle at which they were assumed to be symptomatic (Table 10), they transition to the ‘symptomatic and treated’ health state which was associated with a lower utility (0.71 – same as the previous submission) and costs and disutility associated with nusinersen (drug and adverse event) and also background healthcare costs (\$7,190 per cycle – same overall annual cost of \$14,380 as previous submission). There were effectively no transition

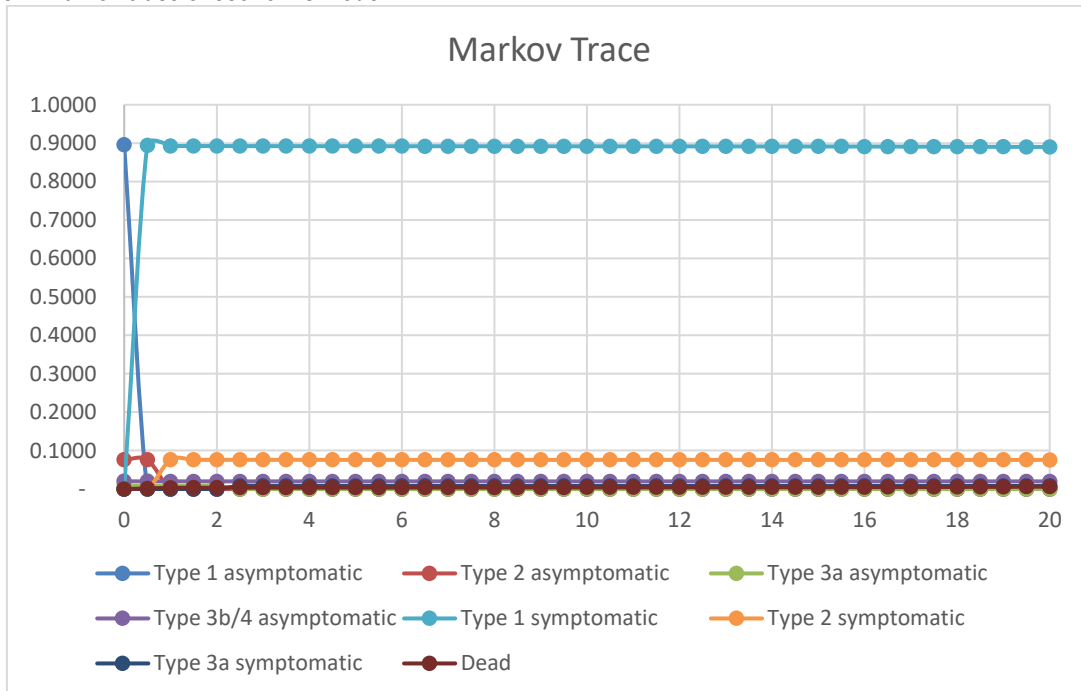
probabilities as the transition probability from ‘asymptomatic and untreated’ to ‘symptomatic and treated’ in the SoC arm was 100% at the assumed age of symptom onset and 0% before the age of onset. Given that SMA is a degenerative disease, it may be unreasonable to assume an immediate decrement of 0.20 in utility as soon as they become symptomatic.

- 6.33 The ESC noted that a cycle length of six months was similar to the dosing frequency of nusinersen of four months however considered that six months may be too long to capture all events for patients with Type I SMA, as some patients with more severe disease may become symptomatic and die within the first six months before the first cycle is over.
- 6.34 Assuming patients will begin treatment as soon as they become symptomatic in SoC may not be reasonable as this does not reflect the current standard of care, since only NSW and ACT have a wide spread newborn screening program for SMA in place currently. Available evidence indicates there is significant delay between symptom onset and diagnosis/treatment. Data provided by the Department of Health for the age of patients initiating nusinersen under the current restriction from 1 June 2018 to 30 December 2018 indicated that at least 65% of patients were aged 5 years or more, and the average age of patients with confirmatory *SMN1* tests in Australia (based on Victorian Clinical Genomic Service (VCGS) data presented in the resubmission) was 13.5 years during the 2013-2018 period. Therefore, it is possible that the resubmission overestimated the treatment duration of nusinersen in the SoC arm, which may favour the pre-symptomatic initiation arm. The ESC considered that while awareness of SMA screening is increasing in clinical practice, equity of access to newborn screening for SMA remains an issue as newborn screening costs in states and territories apart from NSW and ACT are currently borne by public hospitals and private payers. As such, the ESC considered the assumption that patients would begin treatment immediately after becoming symptomatic likely overestimated the treatment duration and cost of nusinersen in the SoC arm.
- 6.35 All patients in the pre-symptomatic initiation treatment arm start in the ‘asymptomatic and treated’ health state, during which they incur costs and disutilities associated with nusinersen (drug and adverse event) treatment but have an asymptomatic utility of 0.91. Patients are never assumed to transition out of the ‘asymptomatic and treated’ health state to the ‘symptomatic and treated’ health state explicitly, but once patients reach the corresponding age/cycle at which they were assumed to be symptomatic (Table 10), they start to accrue a background healthcare cost each cycle (starting at \$5,752 per cycle and increasing by \$36 per cycle up to \$7,190 – the incremental difference between arms was lower than that in the previous submission, which assumed a saving of \$4,380 per annum over a time horizon of 80 years). Patients experience a gradual decline in utility starting from 0.91 and decreasing by 0.05 per cycle down to 0.71 over 4 cycles. This decrease is more conservative than that of the previous submission which assumed no decreasing utility in pre-symptomatic initiation treatment arm. However, the ESC noted that a utility

gain of 0.2 was still based on an assumption and was potentially optimistic, given that the resubmission considered that a utility gain of 0.1 or more for pre-symptomatic initiation of treatment compared to SoC was reasonable based on a naïve comparison of patients in NURTURE and the ENDEAR/SHINE population. The ESC noted that applying a utility gain of 0.1 in the model increased the ICER to \$255,000 to < 355,000/QALY.

- 6.36 In each cycle, independent of treatment or SMA type, patients may die from background mortality, based on ABS life tables for Australians aged 0-20 years (in the previous submission, no deaths from any source were assumed). Given that the life expectancy of patients with Type I SMA is around 2 years, the omission of mortality from SMA was inappropriate and may overestimate the duration of assumed benefit in pre-symptomatic initiation of treatment compared to SoC in Type I SMA. The ESC considered that mortality of Type I SMA patients should be included in the model noting that patients with Type I SMA account for the majority of the cohort modelled (89.56%).
- 6.37 The ESC considered that overall, the model structure did not capture the progressive and degenerative nature of SMA or account for the full spectrum of disease severity due to the absence of transition probabilities, the cycle length applied and omission of SMA related mortality.
- 6.38 A Markov trace of the resubmission's model is presented in Figure 4. The Markov trace is identical for both the pre-symptomatic initiation arm and the SoC arm, with the only difference being that patients in the pre-symptomatic initiation arm were treated from the first cycle whereas patents in the SoC arm were treated as soon as they become symptomatic.

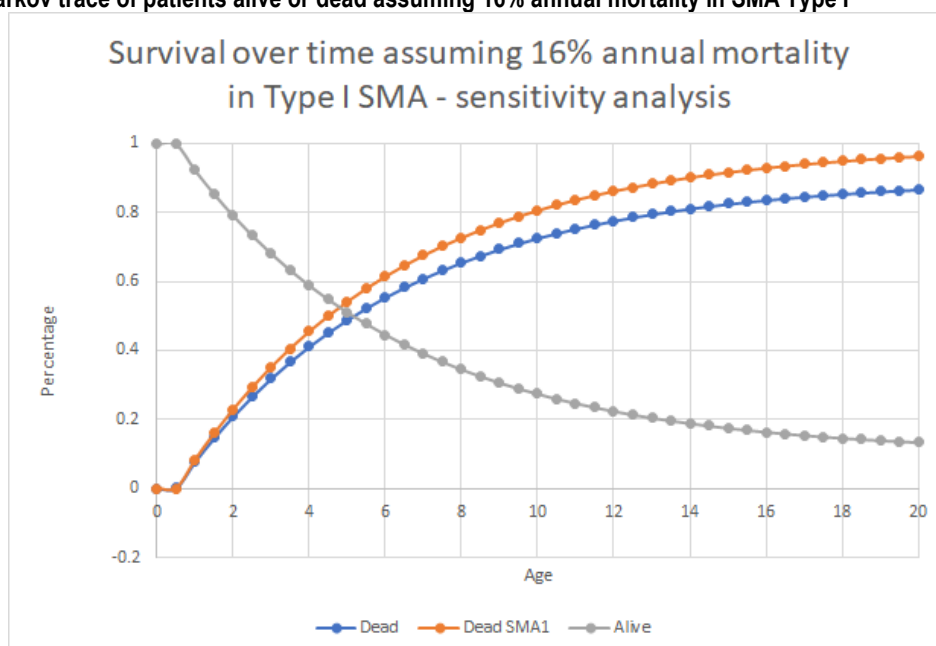
Figure 4: Markov trace of economic model



Source: constructed during evaluation using Nusinersen Economic Model\_March2020

- 6.39 It was inappropriate to assume that patients with Type I SMA would survive for 20 years in the model, given that the published literature reported significant mortality in patients with Type I SMA (See Table 8). The ESC considered that a time horizon of 20 years was still likely optimistic in the context of the available clinical data.
- 6.40 The evaluation considered that a scenario in which an annual mortality of 16% (8.3485% per cycle) as reported in ENDEAR is applied to patients with SMA type I, is likely to be a more realistic representation of the survival of patients with Type I SMA and an *SMN2* copy  $\leq 2$ . This corresponds to a median survival of 4.25 years for patients with Type I SMA and an *SMN2* copy  $\leq 2$  in the model, which was longer than the median of 73.0 weeks for death or permanent ventilation as reported in SHINE from a pooled analysis of 81 patients who have been treated with nusinersen in clinical studies. The Markov trace of alive vs dead patients in this scenario is presented in Figure 5.

Figure 5: Markov trace of patients alive or dead assuming 16% annual mortality in SMA Type I



Source: Constructed during evaluation

6.41 A summary of the key drivers of the model are presented in Table 12.

Table 12: Key drivers of the model

Description	Method/Value	Impact
Utility benefit assumed	Base case assumed utility benefit of 0.2 between treatment arms. This was not supported by any evidence and is purely an assumption. The ICER was approximately linearly proportional to the assumed utility gain (i.e. halving the benefit will double the ICER)	High, favours pre-symptomatic initiation Base case (0.2): \$115,000 to < \$135,000/QALY 0.1: \$255,000 to < 355,000/QALY (+101%) 0.05: \$455,000 to < \$550,000/QALY (+304%)
Duration of utility benefit	Base case assumed utility benefit of 0.2 declines linearly over 20 years to 0. The ICER was sensitive to the duration over which the utility benefit declined	High, favours pre-symptomatic initiation Base case (20 years): \$115,000 to < \$135,000/QALY 10 years: \$155,000 to < 255,000/QALY (+77%) 5 years: \$355,000 to < \$455,000/QALY (+222%)
Mortality from SMA	Base case assumed no mortality from SMA. Using a 16% annual mortality rate for patients with SMA Type I, as reported in nusinersen treated patients in ENDEAR, increases the ICER significantly.	High, favours pre-symptomatic initiation Base case (0% pa): \$115,000 to < \$135,000/QALY 16% pa: \$255,000 to < \$355,000/QALY (+101%)

Source: Table 3-16, p161 and Nusinersen Economic Model\_March2020.xlsx

6.42 In the previous model, duration of early treatment, false positive rates and health state cost savings were all key drivers. In the resubmission, the impact of duration of early treatment and false positive rates were much less significant due to the *SMN2* copy number threshold changing from  $\leq 3$  to  $\leq 2$ . An *SMN2* copy number threshold of  $\leq 2$  resulted in (i) the proportion of each SMA Type changing significantly, with a much higher proportion of SMA Type I, which is associated with a shorter incremental

duration of pre-symptomatic treatment; and (ii) a lower false positive rate. The assumed health state cost savings had a smaller impact on the ICER than in the previous submission and in comparison to other factors listed in Table 11. Additionally, the change in model structure made cross model comparisons of key drivers difficult and uninformative.

- 6.43 The resubmission estimated an ICER of \$45,000 to < \$55,000/QALY. Various errors in the economic model were identified in terms of:
- (i) Application of half cycle corrections: half cycle correction was inappropriately applied to the cost of nusinersen, along with the cost of administration, adverse events as well as utility decrement from adverse events in the first cycle;
  - (ii) Doses in the initiation phase: the resubmission assumed three doses in each of the first two cycles for initiation of nusinersen. This was changed to four doses in the first cycle of initiation, then two doses in the second cycle to more accurately reflect the dosing schedule according to the product information; and
  - (iii) Rebate in the SoC arm: the resubmission did not apply the rebate for ██████████ ██████████ to the SoC arm in patients with Type II and IIIa SMA, treated once becoming symptomatic.

The resulting ICER following correction of these errors was \$115,000 to < \$135,000/QALY. All results (base case and sensitivity analyses) are in reference to this corrected ICER.

6.44 The results of the economic analysis are presented in Table 13.

**Table 13: Result of economic evaluation**

Model parameter	Pre-symptomatic initiation	Standard of Care (SoC)	Incremental (corrected base case)
<b>Costs</b>			
SMN2 test costs	\$1,250	\$0	\$1,250
Nusinersen costs	\$██████████	\$██████████	\$██████████
Admin costs	\$16,894	\$15,894	\$1,000
AE cost <sup>a</sup> s	\$1,225	\$1,022	\$203
HS costs	\$155,976	\$177,163	-\$21,187
<b>Total costs</b>	<b>\$██████████</b>	<b>\$██████████</b>	<b>\$██████████</b>
<b>Outcomes</b>			
QALY	10.7276	9.2542	1.4734
AE QALY loss	-0.0300	-0.0250	-0.0050
<b>Total QALY</b>	<b>10.6976</b>	<b>9.2292</b>	<b>1.4684</b>
		<b>ICER</b>	<b>\$██████████ /QALY</b>
		<b>Previous submission</b>	<b>\$██████████ /QALY<sup>b</sup></b>
		<b>ESC respecified base case ICER</b>	<b>\$██████████ /QALY</b>

Source: constructed during evaluation using Nusinersen Economic Model\_March\_2020

QALY = quality adjusted life years, AE = adverse events, HS = health state, ICER = incremental cost effectiveness ratio

<sup>a</sup> Includes only the cost of management of patients with post lumbar puncture syndrome (38% if age ≤1 year, 4.6% if ≥1 year) which requires hospitalisation (15%)

<sup>b</sup> based on incremental cost of \$██████████ and incremental QALY of 3.7023 over 80 years

*The redacted tables shows ICERS in the range of \$115,000 to < \$135,000/QALY for the current ICER and previous submission; and \$255,000 to < \$355,000/QALY for the ESC respecified base case ICER.*

- 6.45 The estimated ICER was \$55,000 to < \$75,000/QALY for patients with SMA Type I (89.56% of cohort) and \$755,000 to < 855,000/QALY for all other SMA Types (10.44% of cohort).
- 6.46 The ESC considered that the base case ICER should be respecified to include a mortality per annum of 16% for Type I SMA patients with an *SMN2* copy number of 2 (as reported in ENDEAR). Application of the 16% annual mortality for patients with SMA Type I and an *SMN2* copy of 2 resulted in an ICER of \$255,000 to < \$355,000/QALY. The ESC considered that even with the application of mortality, the economic model was still considerably uncertain given the uncertainty around the magnitude of the utility gain and issues around the structure of the model in paragraph 6.37. The pre-PBAC Response noted that application of a 16% per annum mortality for Type I SMA patients results in death of 40% of the pre-symptomatic initiation population despite was there being no deaths in the NURTURE trial at a medial follow up of 3.8 years (45.6 months). In this regard, the pre-PBAC Response argued that the assumption of a 16% per annum mortality for Type I SMA patients is incorrect.
- 6.47 The results of key univariate sensitivity analyses presented by the resubmission and conducted during the evaluation, are summarised in Table 14.

**Table 14: Univariate sensitivity analyses presented by the resubmission.**

Scenario	Incremental cost	Incremental QALY	ICER (\$/QALY)	%Δ
<b>Corrected base case</b>	\$ [REDACTED]	1.4684	\$ [REDACTED]	0%
<i>SMN2</i> ≤3 (base case ≤2)	\$ [REDACTED]	1.3839	\$ [REDACTED]	+141%
Assume 25% saving on health state costs with pre-symptomatic initiation treatment (base case 20%)	\$ [REDACTED]	1.4684	\$ [REDACTED]	-3%
Assume 5% saving on health state costs with pre-symptomatic initiation treatment (base case 20%)	\$ [REDACTED]	1.4684	\$ [REDACTED]	+8%
Assume no decline in utility and cost benefit (base case decline over 20 years)	\$ [REDACTED]	2.4591	\$ [REDACTED]	-45%
Utility benefit last 10 years (base case 20 years)	\$ [REDACTED]	0.8671	\$ [REDACTED]	+77%
Utility benefit last 5 years (base case 20 years)	\$ [REDACTED]	0.4884	\$ [REDACTED]	+222%
Incremental utility benefit 0.05 (base case 0.20)	\$ [REDACTED]	0.3634	\$ [REDACTED]	+304%
Incremental utility benefit 0.10 (base case 0.20)	\$ [REDACTED]	0.7317	\$ [REDACTED]	+101%
Incremental utility benefit 0.29 (base case 0.20)	\$ [REDACTED]	2.1315	\$ [REDACTED]	-31%
Time horizon 5 years (base case 20 years)	\$ [REDACTED]	0.7305	\$ [REDACTED]	+69%
Time horizon 10 years (base case 20 years)	\$ [REDACTED]	1.1825	\$ [REDACTED]	+12%
Time horizon 40 years (base case 20 years)	\$ [REDACTED]	1.4690	\$ [REDACTED]	+12%

Source: Table 3-16, p161 and Nusinersen Economic Model\_March2020.xlsx

QALY = quality adjusted life year, AE = adverse event

Values were calculated during evaluation

*The redacted table shows ICERs in the range of \$55,000 to < \$75,000/QALY, \$75,000/QALY to < \$95,000/QALY, \$115,000 to < \$135,000/QALY, \$135,000 to < \$155,000/QALY, \$155,000 to < \$255,000/QALY, \$255,000 to < \$355,000/QALY, \$355,000 to < \$455,000/QALY, \$455,000 to < \$550,000/QALY.*

- 6.48 The model had a peculiar relationship with the time horizon, where both a shorter (10 year) and longer (40 year) time horizon both lead to an increase in the ICER. The ESC

noted this is due to the model’s assumption that the incremental utility benefit declines linearly over 20 years. At 10 years, compared to the base case, there are still uncaptured benefits from incremental utility between the two treatment arms between Years 11 and 20. Beyond Year 20, there is no longer a utility difference in symptomatic patients between the two arms for patients with Type I SMA, but patients treated in the pre-symptomatic initiation arm who would not be treated under SoC (i.e. patients with Type IIIb/IV SMA) remain on treatment, accruing costs in the pre-symptomatic initiation arm relative to the SoC arm, leading to a higher ICER.

- 6.49 Beyond the 16% annual mortality reported in ENDEAR, a range of annual mortalities were tested during the evaluation. The results are summarised in Table 15 and Figure 4 and Figure 5.

**Table 15: Sensitivity analyses around mortality rate of SMA Type I conducted during evaluation.**

Scenario	Incremental cost	Incremental QALY	ICER (\$/QALY)	%Δ
<b>Corrected base case (no SMA related mortality) – median OS 85.75 years<sup>a</sup></b>	\$ [REDACTED]	1.4684	\$ [REDACTED]	0%
1% annual mortality – median OS 61.75 years	\$ [REDACTED]	1.3976	\$ [REDACTED]	+6%
2% annual mortality – median OS 34.25 years	\$ [REDACTED]	1.3321	\$ [REDACTED]	+12%
5% annual mortality – median OS 13.75 years	\$ [REDACTED]	1.1634	\$ [REDACTED]	+30%
7.5% annual mortality – median OS 9.25 years	\$ [REDACTED]	1.0489	\$ [REDACTED]	+45%
10% annual mortality – median OS 7.25 years	\$ [REDACTED]	0.9530	\$ [REDACTED]	+61%
12.5% annual mortality – median OS 5.75 years	\$ [REDACTED]	0.8722	\$ [REDACTED]	+78%
<b>16% annual mortality as per ENDEAR – median OS 4.25 years (ESC respecified base case)</b>	\$ [REDACTED]	<b>0.7787</b>	\$ [REDACTED]	<b>+101%</b>
20% annual mortality – median OS 3.75 years	\$ [REDACTED]	0.6934	\$ [REDACTED]	+128%
25% annual mortality – median OS 2.75 years	\$ [REDACTED]	0.6102	\$ [REDACTED]	+162%
30% annual mortality – median OS 2.25 years	\$ [REDACTED]	0.5455	\$ [REDACTED]	+195%
40% annual mortality – median OS 1.75 years	\$ [REDACTED]	0.4517	\$ [REDACTED]	+262%
50% annual mortality – median OS 0.75 years	\$ [REDACTED]	0.3870	\$ [REDACTED]	+329%

Source: Constructed during evaluation using Nusinersen Economic Model\_March2020.xlsx

QALY = quality adjusted life year, AE = adverse event, OS = overall survival, yo = years old

<sup>a</sup> Median OS for SMA Type I patient only, estimated by looking for 50<sup>th</sup> percentile in dead state after setting 100% of cohort to SMA type I in model

*The redacted table shows ICERs in the range of \$115,000 to < \$655,000/QALY.*

- 6.50 The survival of SMA Type I patients had a large impact on the estimated ICER, and increasing mortality had an impact on both the incremental cost (smaller cost offsets) and incremental QALY (fewer QALY gains due to reduced life years). However, it was difficult to identify the most appropriate annual mortality for the economic model as there is a paucity of evidence of the long-term survival of patients with SMA Type I and *SMN2* copy ≤2 treated with nusinersen. In the absence of long-term survival data, it was likely most appropriate to apply the 16% annual mortality reported in patients with SMA Type I and an *SMN2* copy of 2 treated with nusinersen in ENDEAR (n=80). The PSCR argued that applying a constant 16% mortality per annum is unreasonable as no additional patients in the ENDEAR and SHINE studies died beyond 78 weeks. The PSCR stated that the omission of SMA related mortality was a conservative approach given that no benefit in overall survival with pre-symptomatic treatment was claimed

in the resubmission. The ESC considered that the omission of SMA related mortality was not a conservative approach noting the results of the economic analysis are driven by the lack of SMA related mortality. The ESC considered that a median OS of 87.75 years was not supported by the clinical data and that a median OS of 4.25 years (when the 16% mortality per annum is applied) was more reflective of the available evidence.

6.51 A range of multivariate sensitivity analyses were presented by the resubmission. These multivariate sensitivity analysis were also conducted assuming 16% annual mortality in SMA Type I during the evaluation. The results of these analyses are summarised in Table 16.

**Table 16: Multivariate sensitivity analysis presented by the resubmission**

Treatment benefit (utility gain)	Health state cost saving	ICER /QALY by duration of treatment effect					
		5 years		10 years		20 years (Base case)	
<b>No mortality from SMA<sup>a</sup></b>							
0.1	5%						
	10%						
	20% (base case)						
0.2 (base case)	5%						
	10%						
	20% (base case)						
<b>Assume 16% annual mortality in SMA Type I<sup>b</sup></b>							
0.1	5%						
	10%						
	20% (base case)						
0.2 (base case)	5%						
	10%						
	20% (base case)						

Source: Table 3-17, p162 and Constructed during evaluation using Nusinersen Economic Model\_March2020.xlsx

<sup>a</sup> Values have been corrected during the evaluation

<sup>b</sup> Calculated during the evaluation

The redacted table shows ICERs in the range of \$115,000 to > \$1,055,000/QALY.

### Drug cost/patient/ year

**Table 17: Drug cost per patient for proposed and comparator drugs**

	Pre-symptomatic initiation			SoC		
	Study dose and duration	Model	Financial estimates	Study dose and duration	Model	Financial estimates
Mean dose	12mg at days 0, 14, 28 and 63, then every 4 months after confirmed SMN1 deletion/mutation			12mg at days 0, 14, 28 and 63, then every 4 months after onset of at least 2 SMA symptoms		
Mean duration	Life long					
Cost/patient/dose	\$					
Cost/patient/year	Initiation: \$ /year Maintenance: \$ /year			Initiation: \$ <sup>a</sup> /year Maintenance: \$ /year		

Source: Constructed during evaluation

<sup>a</sup> There is a rebate for [redacted] for patients with Type II and IIIa SMA under the current Deed of agreement, but this was not included in either of the resubmission's economic model or financial estimates

SoC = standard of care

6.52 The drug cost of nusinersen was \$ [redacted] for the four initial loading doses and \$ [redacted] per year thereafter for maintenance, based on the effective price of \$ [redacted] per 12mg dose.

- 6.53 In the resubmission, the incremental mean duration of treatment from pre-symptomatic initiation of treatment compared to SoC can be estimated from the economic model by removing the rebate for SMA Type II and IIIa in the SoC arm (from the corrected base case), changing the discounting rate to zero, then dividing the incremental drug cost (\$██████) by the cost per unit of nusinersen (\$██████). This gives a result of 2.93 doses, or 11.71 months/0.98 years, which was marginally longer than the 0.91 year applied in the model in the previous submission. The PBAC had previously considered that an incremental duration of treatment of 0.91 years for pre-symptomatic initiation (which was rounded up to 1 year in the model) was underestimated and therefore the resubmission's estimate may also represent an underestimate of the incremental duration of treatment for patients treated with pre-symptomatic initiation compared to SoC. However, given the difference in the proportion of each SMA types in the assumed cohort, the incremental duration of treatment may not be comparable between the resubmission and the previous submission.

***Estimated PBS usage & financial implications***

- 6.54 The resubmission was not considered by DUSC. The resubmission used an epidemiological approach for the financial estimates for the listing of nusinersen for pre-symptomatic initiation.
- 6.55 For the financial estimates, the resubmission assumed that all newborn babies in Australia will be screened for SMN1 mutation though the resubmission is not seeking funding for screening. The ESC considered this was not an appropriate assumption given issues of access to screening remain (see paragraph 6.34). The PBAC considered that there is an equity issue as newborn screening costs in States and Territories apart from NSW and ACT are currently borne by public hospitals and private payers, with the cost of the SMN1 test being \$220 and the cost of the SMN2 copy number test being \$350 based on VCGS prices (paragraph 11.9, nusinersen, Addendum to the July 2019 PSD, November 2019 PSD). DUSC (paragraph 6.48, nusinersen, PSD, July 2019) previously noted that screening rates will likely increase if pre-symptomatic initiation of nusinersen was PBS listed. The assumption that all newborns are screened for SMN1 mutation resulted in much earlier treatment in the SoC arm, which potentially overestimate the cost offsets in the SoC arm. Based on the estimated live births from ABS projections and assuming a cost of \$220 per test as per the VCGS website, the estimated cost of screening for SMN1 mutation for the rest of Australia (excluding ACT and NSW) would be between \$49.5 million to \$53.0 million per annum from 2021 to 2026.
- 6.56 Although the resubmission requested a grandfathering restriction, no grandfathered patients were included in the financial estimates. The pre-PBAC Response confirmed that only < 500 patient was currently receiving nusinersen free of charge and this patient would not be eligible for grandfather treatment (see paragraph 3.7).

**Table 18: Key inputs for financial estimates**

Parameter	Value and source					Comment	
Eligible patients	Estimate < 500 new SMA patients per year, with <500 eligible for pre-symptomatic initiation of treatment					The ESC noted this is overestimated as it is based on all newborn babies being screened.	
Distribution of SMN2 copy number for each SMA type	<b>SMA type</b>					The proportion of Type I SMA patients estimated (34.08% overall) was much higher than the proportion of Type I SMA patients treated on the PBS under the current restriction between 1 June 2018 to 30 December 2018 (7/74, 9.5%) Should the proportion of Type I SMA be overestimated, the financial estimates will be underestimated. Base case includes only SMN2 copy of 1 and 2.	
	<b>SMN2 copy</b>	<b>I</b>	<b>II</b>	<b>IIIa</b>	<b>IIIb</b>		<b>IV</b>
	1	1.69%	0.11%	0.00%	0.00%		0.00%
	2	23.40%	2.02%	0.22%	0.56%		0.00%
	3	8.89%	30.26%	10.12%	3.71%		0.00%
	4	0.11%	2.14%	5.51%	10.01%		0.67%
	5+	0.00%	0.00%	0.00%	0.56%		0.00%
All	34.08%	34.53%	15.86%	14.85%	0.67%		
Source: Biogen B1 effective price sheet, Nusinersen Section 4_March2020.xlsx							
Dosages of nusinersen	Pre-symptomatic initiation, all patients: 6 doses per year for initiation first year (incident patients), 3 doses per year for maintenance thereafter (prevalent patients), based on product information  SoC, Type I: onset at 6 months, therefore 3 doses in year 1 and 4.5 doses in year 2 then 3 doses per year thereafter SoC Type II: onset at 1 year, 5 doses in year 1 (includes rebate [REDACTED]), and 3 doses per year thereafter SoC Type III: onset at 2.25 years, 3.75 doses in year 1, 3.50 doses in year 2, 3 doses per year thereafter.					Assumption that patients begin treatment at symptom onset will overestimate cost offsets in SoC. All evidence points to a delay between symptom onset and treatment initiation. The age of assumed onset are reasonably consistent with the diagnostic criteria for Type I SMA (onset 0-6 months) and Type II SMA (<18 months) and Type IIIa SMA (<3 years)	
Beneficiary type	Assume 39% of use by general patients, with 61% in concession category.					Reasonable. However co-payments not considered in financial estimates, which is conservative and overestimates the financial estimates, albeit by a very minor margin.	
Nusinersen costs	\$ [REDACTED] per dose.					Consistent with economic evaluation.	
Cost of Adverse Event treatment	Assume 15% of patients will need hospitalisation for PLPS in 38% of patients treated with nusinersen at a cost of \$1,839 per episode					Consistent with economic evaluation. Applied to all age groups and may be more conservative than economic evaluation	
Nusinersen administration	Resource	MBS item	Unit cost applied	Unit cost current		There is a minor difference between the unit costs applied in the resubmission and the current MBS benefits. However the magnitude of difference is minor relative to the cost of nusinersen.	
	Specialist consultation	105	\$43.65	\$44.35			
	Pre-anaesthesia consultation	17610	\$43.65	\$44.35			
	Initiation of anaesthesia for lumbar puncture	21945	\$99.00	\$100.50			
	Anaesthesia for <15 minutes	23010	\$19.80	\$20.10			
	Intrathecal infusion	18216	\$189.90	\$192.95			
	Total admin cost	-	\$396.00	\$402.25			
Source: Table 4-12, p172. Costs reflect 100% MBS benefits							

Source: constructed during evaluation using information from Nusinersen Economic Model\_March2020, p165-169 of the resubmission. PLPS = post-lumbar puncture syndrome

6.57 The financial estimates for extending the listing of nusinersen to include pre-symptomatic initiation of treatment with nusinersen in patients with *SMN1* deletion or mutation and *SMN2* copy number ≤2 are summarised in Table 19. Additionally,

results from the previous submission and a scenario assuming a threshold of *SMN2* copy number  $\leq 3$  were also presented for comparison.

**Table 19: Estimated use and financial implications**

	2021	2022	2023	2024	2025	2026
<b>Estimated extent of use</b>						
Total incident patients						
Total scripts dispensed <sup>a</sup>						
<b>Estimated financial implications of pre-symptomatic initiation of nusinersen</b>						
Drug cost nusinersen (PBS/RPBS)	\$	\$	\$	\$	\$	\$
<b>Total cost pre-symptomatic initiation <sup>b</sup></b>	\$	\$	\$	\$	\$	\$
Previous submission	\$	\$	\$	\$	\$	\$
Doses used by Type IIIb (leakage)	0.98	1.49	2.00	2.53	3.05	3.58
Cost for Type IIIb (leakage)	\$	\$	\$	\$	\$	\$
<b>Estimated financial implications for SoC</b>						
Total scripts under SoC (Cost offset)	21.9	58.23	83.19	108.46	133.99	159.78
Total cost SoC (Cost offset)	\$	\$	\$	\$	\$	\$
Previous submission	\$	\$	\$	\$	\$	\$
<b>Net financial implications</b>						
Net Cost to PBS/RPBS	\$	\$	\$	\$	\$	\$
Net Cost to MBS	\$	\$	\$	\$	\$	\$
Total cost pre-symptomatic	\$	\$	\$	\$	\$	\$
Total cost SoC	\$	\$	\$	\$	\$	\$
<b>Net cost to government</b>	\$	\$	\$	\$	\$	\$
Previous submission	\$	\$	\$	\$	\$	\$
<i>SMN2</i> threshold $\leq 3$	\$	\$	\$	\$	\$	\$

Source: Table 4-6, p169, Table 4-7, p170, Table 4-8, p170, Table 4-9, p171, Table 4-10, p172, Table 4-13, p173, Table 4-14, p174 and Table 4-17, p176 of the resubmission, Table 4.2.6, 6.05.COM.82, Table 4.3.1, 6.05.COM.83 and Table 4.5.5, 6.05.COM.87, nusinersen July 2019 commentary, additional information extracted from Nusinersen Economic Model\_March2020, p165-169 of the resubmission.

SoC = standard of care

<sup>a</sup> All patients assumed will use 6 scripts per year for initiation first year (incident patients) and 3 scripts per year for maintenance thereafter (prevalent patients), based on product information. Estimate assumes no mortality

<sup>b</sup> Includes MBS administration costs, hospitalisation costs for management of post lumbar puncture syndrome and cost of *SMN2* copy number testing for patients who were not eligible for pre-symptomatic treatment (i.e. copy number  $\geq 3$ )

*The redacted table shows that at Year 6, the estimated number of total incident patients was < 500; the estimated number of scripts dispensed was < 500 and the net cost to government in this submission, the previous submission and *SMN2* threshold  $\leq 3$  would be \$0 to < \$10 million.*

6.58 The total cost to the PBS/RPBS of extending the listing of nusinersen to include pre-symptomatic initiation of treatment was estimated to be \$0 to < \$10 million in Year 6, and a total of \$0 to < \$10 million in the first 6 years of listing.

6.59 The cost offsets may be overestimated due to the assumption that patients in SoC will initiate treatment as soon as they become symptomatic. The ESC noted that cost offsets from SoC treatment were not true cost savings but rather a shifting of costs to earlier if nusinersen was listed for pre-symptomatic initiation of treatment. The ESC further noted that the estimates are based on all newborn babies in Australia being screened which is currently not the case.

- 6.60 The pre-PBAC Response stated that SMN1 testing costs were omitted from the financial estimates as this test is only offered to infants suspected to be at risk of SMA and would be conducted irrespective of the availability of nusinersen for pre-symptomatic initiation of treatment.
- 6.61 The overall financial impact in the resubmission was lower than the previous submission as:
- i) The previous submission assumed a higher *SMN2* threshold of  $\leq 3$  compared to  $\leq 2$  in the current resubmission; and
  - ii) Using an alternative distribution of *SMN2* by SMA type, the previous submission estimated far more Type II and IIIa patients (7 and 3 by Year 6, respectively) than the current resubmission (0.66 and 0.07, respectively). The additional number of doses used in pre-symptomatic initiation for Type II (4 doses in previous submission, average 4.35 in current resubmission) and Type IIIa (7 and 7.5 doses, respectively) were significantly higher than in Type I (1 and 1.5 doses, respectively).
- 6.62 The resubmission also presented sensitivity analyses around the financial estimates assuming an *SMN2* copy number threshold of  $\leq 3$ , same as the previous submission. The estimated cost per year increased to \$0 to < \$10 million by year 6 and \$50 to < \$60 million in the first 6 years of listing. These estimates were higher than the previous submission due to differences listed in paragraph 6.61 and the previous submission assumed much lower uptake of screening (30% in Year 1 and 2, 50% in Year 3, 80% in Year 4 and then 100% thereafter) in the first four years of listing, leading to smaller patient numbers and lower financial estimates

### **Quality Use of Medicines**

- 6.63 No quality use of medicines issues were identified. Given the lack of evidence available, consideration with regards to collection of real world data may be relevant to the current resubmission.

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

- 6.64 The sponsor proposed that the expenditure caps specified in the current Deed of Agreement for nusinersen remain unchanged, but that the Deed of Agreement be amended to include the cost of patients treated under pre-symptomatic initiation.
- 6.65 Additionally, the sponsor stated that the cost associated with any potential use of nusinersen in patients who would otherwise never become eligible for treatment under the current PBS restriction be rebated to the Government, but no further details were provided. The cost of pre-symptomatic initiation of nusinersen in patients with Type IIIb and IV SMA were included in the costs presented in the resubmission, with no mention of any rebates. In the previous submission, the Sponsor proposed that the cost of patients treated under the proposed restriction who would not have developed symptoms by the age of 3 years could be borne by the sponsor via an appropriate mutually agreed funding mechanism.

- 6.66 The PSCR requested that the existing expenditure caps for nusinersen be adjusted to account for pre-symptomatic initiation of treatment as earlier dosing is expected to impact expenditure in each 12 month period. The ESC considered that any addition to the existing caps to account for pre-symptomatic initiation of treatment should not be made without a decrease in the existing caps proportional to the cost for patients estimated to be treated with nusinersen under the current listing that would be expected to shift to pre-symptomatic initiation of treatment.

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

## **7 PBAC Outcome**

- 7.1 The PBAC recommended the addition of pre-symptomatic initiation to the current listing of nusinersen to include the pre-symptomatic initiation of treatment of patients genetically diagnosed with SMA, who have an SMN2 copy number of  $\leq 2$ . The PBAC considered that pre-symptomatic initiation of treatment with nusinersen would provide an additional benefit for some patients compared with initiation upon development of symptoms. The PBAC noted there was remaining uncertainty regarding the cost-effectiveness of presymptomatic initiation of nusinersen due to the uncertain magnitude of incremental benefit compared to symptomatic treatment. However, the PBAC was satisfied that extension of the current listing would be adequately cost-effective if the conditions specified in the existing Deed of Agreement were also applied to the extended listing.
- 7.2 The PBAC welcomed the consumer comments from patients, health professionals and organisations. The PBAC acknowledged that the current requirement for symptoms to develop prior to accessing subsidised treatment could have a significant burden on the families of infants genetically diagnosed with SMA.
- 7.3 The PBAC recalled that MSAC considered the prognostic value was more reliable for infants with an SMN2 copy number of  $\leq 2$ . The PBAC also recalled that it previously considered it may be appropriate to restrict any future listing of nusinersen for the pre-symptomatic initiation of treatment to those with  $\leq 2$  or less copies of SMN2 to manage the risk of overtreatment (i.e. treatment of patients who would have otherwise developed type IIIb or IV SMA).
- 7.4 The PBAC noted the February 2020 interim analysis of the NURTURE trial presented in the pre-PBAC Response, which represented a median follow-up of 3.8 years. The PBAC noted at the time of the interim analysis, all patients (n=25) remained on treatment without requirement for permanent ventilation and that there were no deaths. The PBAC also noted there was no loss of major motor milestones for any patients. The PBAC considered that while the updated data provided some assurance in the durability of response, the magnitude of incremental benefit compared with symptomatic treatment over a lifetime remains uncertain. The PBAC noted that comparative long-term data that would address this uncertainty was unlikely to be available in the future.

- 7.5 The PBAC noted that no new safety signals from the NURTURE trial were identified at a median follow-up of 3.8 years. The PBAC noted that the safety of a lifetime treatment with nusinersen was unknown.
- 7.6 The PBAC noted that the revised economic analysis used a time horizon of 20 years and incorporated an assumption of a 0.2 utility gain, which decreased linearly to 0 over the time horizon. The PBAC noted that the ICER (corrected for errors) was estimated to be \$115,000 to < \$135,000/QALY. The PBAC considered that while the revised economic model was more conservative than that of the previous submission, there was remaining uncertainty regarding the estimated ICER as the model inputs were assumptions. The PBAC noted the ICER was sensitive to the survival of SMA type I patients, who are estimated to account for the majority (89.56%) of patients with an SMN2 copy number of  $\leq 2$  and that the ICER increased to \$255,000 to \$355,000/QALY when a 16% annual mortality was applied to SMA type I patients. The PBAC considered that the most appropriate mortality rate to apply to SMA Type I patients in the model was uncertain given the lack of long-term data however, considered that the omission of SMA related mortality from the model likely overestimated survival, noting median OS is 85.75 years in the resubmission's base case. The PBAC also noted that the ICER was sensitive to the assumed utility gain and that the assumption of a linear decrease in utility gain over the 20-year time horizon resulted in the ICER increasing with both a shorter and longer time horizon. Overall, the PBAC was uncertain that the model structure accurately reflected the progression of SMA. In light of these uncertainties, the PBAC advised that the rebate of [REDACTED], which currently applies for symptomatic treatment of SMA Type II or IIIa, would need to be extended to all patients who initiate treatment prior to the onset of symptoms, to achieve cost-effectiveness in this treatment setting.
- 7.7 The PBAC noted the total estimated cost of extending the listing of nusinersen to include pre-symptomatic initiation of treatment, was \$0 to < \$10 million over the first 6 years of listing. The PBAC considered that the uncertainties in the financial estimates could be managed by including the extended listing in the current Risk Sharing Arrangement in place for nusinersen. The PBAC advised that any adjustments to the current caps to account for pre-symptomatic initiation of treatment should be made in conjunction with a corresponding decrease to account for patients who would have received treatment under the current listing.
- 7.8 The PBAC noted that access to newborn screening for SMA remained an outstanding issue as only NSW and ACT have a newborn screening program for SMA in place currently. Further, the PBAC noted that implementation of any screening program was the responsibility of individual states and territories and as such, Australia wide availability of newborn screening for SMA may not be available for some time. However, the PBAC acknowledged that overall, the clinical management and diagnosis of SMA was evolving with increasing awareness of SMA. Nevertheless, the PBAC advised that, reflecting ESC's advice, the adjustment to the RSA caps should reflect the

current newborn screening practice rather than be based on the submission’s assumption of nation-wide newborn screening.

- 7.9 The PBAC advised that pre-symptomatic initiation of treatment should be limited to patients less than three years of age.
- 7.10 The PBAC considered it would be appropriate to limit the maximum quantity to one pack with no repeats for continuing treatment, consistent with the current listings.
- 7.11 The PBAC noted that this submission is not eligible for an independent review as it received a positive recommendation.
- 7.12 The PBAC found that the criteria prescribed by the *National Health (Pharmaceutical and Vaccines – Cost Recovery) Regulations 2009* for Pricing Pathway A were not met. Specifically, the PBAC found that in the circumstances of its recommendation for nusinersen:
- a) The treatment is expected to provide a substantial and clinically relevant improvement in efficacy over SoC;
  - b) The treatment is not expected to address a high and urgent unmet clinical need; and
  - c) It was not necessary to make a finding in relation to whether it would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A because one or more of the preceding tests had failed.

**Outcome:**

Recommended

## 8 Recommended listing

8.1 Add new PBS indication with one new treatment phase as follows:

Medicinal Product Pack (Name, form & strength and pack size)	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
NUSINERSEN nusinersen 12 mg/5 mL injection, 5 mL vial	11363C (Public) 11472T (Private)	1	1	3	Spinraza

**Restriction Summary [New]:**

<b>Category/Program:</b> Section 100 – Highly Specialised Drugs Program (Public/Private)
<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners
<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required - non-immediate/delayed assessment by Services Australia (in-writing only via mail/postal service or electronic upload to Hobart)
<b>Episodicity:</b> [blank]
<b>Severity:</b> Asymptomatic

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<b>Condition:</b> spinal muscular atrophy (SMA)
<b>PBS Indication:</b> Asymptomatic spinal muscular atrophy (SMA)
<b>Treatment phase:</b> Initial treatment of asymptomatic SMA – Loading doses
<b>Treatment criteria:</b>
Must be treated by a specialist medical practitioner experienced in the diagnosis and management of SMA associated with a neuromuscular clinic of a recognised hospital in the management of SMA; or in consultation with a specialist medical practitioner experienced in the diagnosis and management of SMA associated with a neuromuscular clinic of a recognised hospital in the management of SMA.
<b>Clinical criteria:</b>
The condition must have genetic confirmation of 5q homozygous deletion of the <i>survival motor neuron 1 (SMN1)</i> gene; or
The condition must have genetic confirmation of deletion of one copy of the <i>SMN1</i> gene in addition to a pathogenic/likely pathogenic variant in the remaining single copy of the <i>SMN1</i> gene
<b>AND</b>
<b>Clinical criteria:</b>
The condition must have genetic confirmation that there are 1 to 2 copies of the <i>survival motor neuron 2 (SMN2)</i> gene
<b>AND</b>
<b>Clinical criteria:</b>
The condition must be asymptomatic
<b>AND</b>
<b>Clinical criteria:</b>
The treatment must be given concomitantly with standard of care for this condition.
<b>AND</b>
<b>Clinical criteria:</b>
The treatment must not exceed four loading doses (at days 0, 14, 28 and 63) under this restriction.
<b>Population criteria:</b>
Patient must be <del>3 years of age or</del> under 36 months prior to commencing treatment.
Application for authorisation of initial treatment must be in writing (lodged via postal service or electronic upload) and must include: (a) a completed authority prescription form; and (b) a completed Asymptomatic spinal muscular atrophy PBS Authority Application - Supporting Information Form which seeks the following: (i) confirmation of genetic diagnosis of SMA; and (ii) a copy of the results substantiating the number of <i>SMN2</i> gene copies determined by quantitative polymerase chain reaction (qPCR) or multiple ligation dependent probe amplification (MLPA);
An outcome on the authority application is not immediate, but will follow in due course. Electronic upload is encouraged to reduce processing time.
<b>Prescriber Instructions:</b> Recognised hospitals in the management of SMA are Queensland Children's Hospital (Brisbane), Royal Children's Hospital Melbourne, Monash Children's Hospital (Melbourne), John Hunter Hospital (Newcastle), Sydney Children's Hospital Randwick, Children's Hospital at Westmead, Adelaide Women and Children's Hospital and Perth Children's Hospital.
<b>Administrative Advice:</b> Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).
Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at <a href="http://www.servicesaustralia.gov.au">www.servicesaustralia.gov.au</a>
Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at <a href="http://www.servicesaustralia.gov.au/hpos">www.servicesaustralia.gov.au/hpos</a> Or mailed to:
Services Australia Complex Drugs Reply Paid 9826 HOBART TAS 7001

<b>Administrative Advice:</b> No increase in the maximum quantity or number of units may be authorised.
<b>Administrative Advice:</b> No increase in the maximum number of repeats may be authorised.
<b>Administrative Advice:</b> Special Pricing Arrangements apply.

8.2 Flow-on changes to the current nusinersen listings are outlined as follows:

**Initial treatment:**

Restriction summary 7854/Treatment of Concept 7849; PBS item codes: 11363C (Public)/ 11472T (Private)

(i) Edit indication to make it easily distinguishable from the new asymptomatic indication:

<b>Episodicity:</b> <i>Symptomatic</i>
<b>Severity:</b> <i>Type I, II or IIIa</i>
<b>Condition:</b> <del>S</del> spinal muscular atrophy (SMA)
<b>Indication:</b> <i>Symptomatic Type I, II or IIIa spinal muscular atrophy (SMA)</i>

(ii) Edit the treatment phase description to distinguish it from that described for asymptomatic patients

<b>Treatment Phase:</b> <i>Initial treatment of symptomatic Type I, II or IIIa SMA - Loading doses</i>
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(iii) Edit the clinical criterion mentioning the SMN1 gene for further clarity and technical correctness:

<b>Clinical Criterion</b>
The condition must <del>5q homozygous deletion, mutation of, or compound heterozygous mutation in the SMN1 gene of type I, II or IIIa;</del> have genetic confirmation of 5q homozygous deletion of the <i>survival motor neuron 1 (SMN1)</i> gene; or
The condition must have genetic confirmation of deletion of one copy of the <i>SMN1</i> gene in addition to a pathogenic/likely pathogenic variant in the remaining single copy of the <i>SMN1</i> gene

(iv) Update Prescriber Instruction for electronic upload option:

<p><b>Prescriber instructions:</b>  Application for authorisation of initial treatment must be in writing (<i>lodged via postal service or electronic upload</i>) and must include:  (a) a completed authority prescription form; and  (b) a completed Spinal muscular atrophy PBS Authority Application - Supporting Information 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).</p> <p><i>An outcome on the authority application is not immediate, but will follow in due course. Electronic upload is encouraged to reduce processing time.</i></p>
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**Continuing treatment:**

Restriction summary 10194/Treatment of Concept 10112; PBS item codes: 11378W (Public)/ 11476B (Private)

(i) Edit the treatment phase description to make it clear that the listing covers continuing treatment in both the SMA Type I, II, IIIa patient and the asymptomatic patient:

<p><b>Treatment Phase:</b> Continuing/maintenance treatment – <del>Maintenance</del> of either symptomatic Type I, II or IIIa SMA or of a patient commenced on this drug under the asymptomatic SMA listing</p>
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(ii) Update the administrative advice to mention Services Australia in place of the Department of Human Services:

<p>Authority applications for continuing treatment may be made by telephone to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).</p>
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<p>Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see <a href="http://www.servicesaustralia.gov.au/HPOS">www.servicesaustralia.gov.au/HPOS</a>) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).</p>
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***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

Biogen welcomes the positive recommendation for nusinersen for the treatment of patients with pre-symptomatic Spinal Muscular Atrophy (SMA). Biogen is committed to pursuing every opportunity to make nusinersen accessible to all those patients in the SMA community who could benefit from it.

As part of post-PBAC processes, Biogen will propose the use of terminology 'pre-symptomatic' in the PBS restriction as this terminology is clinically accurate in describing the disease state of patients enrolled in the NURTURE study.