

7.04 NUSINERSEN, Solution for injection 12mg in 5mL, Spinraza[®], Biogen Australia Pty Ltd

1 Purpose of resubmission

- 1.1 The resubmission requested an extension to the current Section 100 (Highly Specialised Drugs Program) Authority Required listing for initiation and continuation of nusinersen for the treatment of spinal muscular atrophy (SMA) in patients with symptom onset prior to 19 years of age, and removal of the age limit of 18 years for initiation of treatment.
- 1.2 The extension of listing was requested on the basis of a cost-effectiveness analysis of nusinersen and standard of care versus standard of care alone in adult patients aged more than 18 years with Types II and III SMA initiating 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	Treatment of adult patients with at least two of the defined signs and symptoms of SMA Type I, II or III prior to 19 years of age ^a .
Intervention	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
Comparator	<u>Natural history of SMA with standard of care.</u>
Outcomes	Primary endpoint: <ul style="list-style-type: none"> Change from baseline in HFMSE score Secondary endpoint: <ul style="list-style-type: none"> Change from baseline in RULM score Other: <ul style="list-style-type: none"> Percentage of patients achieving motor milestone responses (≥ 3 increase in HFMSE score; ≥ 2 increase in RULM score) Change from baseline in 6MWT Safety
Clinical claim	Nusinersen has superior efficacy and <u>non-inferior safety</u> compared to <u>standard of care.</u>

Source: Table 1.2, p36 of the resubmission.

SMA, spinal muscular atrophy; HFMSE, Hammersmith Functional Motor Scale-Expanded; 6MWT, 6 minute walk test; RULM, revised upper limb module

Note: Underlined text refers to differences and/or patient populations that were not included in the November 2017 PBAC submission, where the comparator was placebo and the claim was no worse in terms of comparative safety

^a The resubmission also requested listing in patients aged <18 years, where symptoms only developed after the patient turned 3 years of age (SMA Type IIIb).

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

2 Background

Registration status

- 2.1 Nusinersen was TGA registered for the treatment of 5q spinal muscular atrophy (SMA) on 2 November 2017.

Previous PBAC consideration

- 2.2 This was the first resubmission for the requested patient population. The previous submission was first considered at the November 2017 PBAC meeting. This was for a broad population comprising patients with infantile-onset (Type I) and childhood-onset (Types II & Type III) SMA with no restrictions proposed regarding the age of nusinersen commencement.
- 2.3 A minor submission was also considered at the March 2018 PBAC meeting. The minor March 2018 submission for symptomatic SMA patients was originally submitted for patients aged 18 years or less with Type I SMA only, however following input and discussion from clinical experts, the requested patient population was expanded to patients aged 18 years or less with Type I, II or IIIa SMA, where the patient had two of the defined signs and symptoms of SMA prior to 3 years of age (with age of onset being a defined sign/symptom). At this meeting, nusinersen received a positive recommendation from the PBAC and was listed for the treatment of patients aged 18 years or less at initiation of treatment, who have had at least two of the defined signs and symptoms of SMA Type I, II or IIIa prior to 3 years of age.
- 2.4 This resubmission is for the patient population included in the submission for the November 2017 PBAC meeting, who are not currently able to access nusinersen on the PBS under the current listing. For this patient population, the key matters of concern from the November 2017 PBAC meeting are summarised in Table 2.

Table 2: Summary of key matters of concern

Component	Matter of concern (November 2017)	How the resubmission addresses it
Clinical effectiveness	There was a lack of randomised comparative evidence for patients with Type III SMA compared to sham-control (the comparator) and the naive comparison of data from 25 patients in the single-arm non-randomised CS12 study versus the natural history of the disease was not sufficient (para 6.38, 7.14)	Not addressed. No new relevant randomised controlled trials were identified. Single-arm data on nusinersen in a greater number of patients was provided.
	Long-term efficacy with nusinersen is uncertain (para 7.15)	Not addressed.
Cost-effectiveness	A cost per responder approach was not justified, and use of utility values to estimate QALYs was preferable (para 6.52)	Addressed by using literature-based utility values from a study funded by the sponsor (Lloyd 2019)
	The PBAC considered that the submission contained insufficient information for the Committee to form a view on the cost-effectiveness of treatment across the spectrum of SMA (para 7.1)	Partially addressed. Incremental cost/QALY gained presented.
	The PBAC considered that the cost per responder estimates presented for Type II and Type III SMA were highly uncertain (para 7.20).	Incremental cost/QALY gained presented
	The PBAC advised that a resubmission presenting a model based on a cost-utility analysis for Types II and III SMA would be required to establish the cost-effectiveness of treatment compared with standard care. Additionally, the PBAC considered that a substantial price reduction would likely be required to render nusinersen cost-effective in the overall SMA population [para 7.21].	For adult patients initiating treatment, the submission proposed a vial price of \$██████, with ██████████ rebated. For non-adult patients with Type IIIb SMA, the existing listed price (\$██████) was requested in Table 1.5 of the resubmission
Financial estimates	The PBAC considered that the patient numbers were underestimated, and particularly the number of patients over the age of 18 years (para 7.4)	Not addressed, although a risk share arrangement with expenditure caps was proposed

Source: November 2017 Public summary document (PSD) for nusinersen.
Paragraph references refer to the November 2017 PSD for nusinersen.

2.5 In July 2020, nusinersen was recommended for treatment initiation in patients with genetically diagnosed pre-symptomatic SMA with SMN2 copy number of 1 or 2.

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

3 Requested listing

3.1 The listing requested by the resubmission is outlined below. Underlined and strikethrough text indicate changes compared with the existing PBS listing.

Public Summary Document – November 2020 PBAC Meeting

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 (published) \$██████ (effective price)	Spinraza, Biogen Australia Pty Ltd
Continuing treatment 12mg*/5mL injection, 1 x 5 mL vial	1	2	\$110,000 (published) \$██████ (effective price)	
Category / Program:	Section 100 – Highly Specialised Drugs Program			
Prescriber type:	<input checked="" type="checkbox"/> Medical Practitioners			
Condition:	Spinal muscular atrophy (SMA)			
PBS Indication:	Treatment of SMA			
Treatment phase:	Initial – New patients			
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:	The condition must be <u>5q</u> homozygous deletion, mutation of, or compound heterozygous mutation in the SMN1 gene of type I, II or III <u>III</u> ; AND Patient must have experienced at least two of the defined signs and symptoms of SMA type I, II or III <u>III</u> prior to <u>3</u> <u>19</u> years of age 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.			
Administrative Advice:	Special Pricing Arrangements apply. No increase in the maximum number of repeats may be authorised.			
Treatment phase:	Continuing treatment			
Restriction:	<input checked="" type="checkbox"/> Authority Required - In Writing			
Clinical criteria:	Patient must have previously received PBS-subsidised treatment with this drug for this condition AND The treatment must be given concomitantly with standard of care for this condition AND The treatment must be ceased when invasive permanent assisted ventilation is required in the absence of a potentially reversible cause while being treated with this drug** <u>or</u> when further treatment is deemed futile.			

* resubmission refers to the strength as 12.6mg/5mL

** in alignment with the current PBS restriction, invasive permanent assisted ventilation means ventilation via tracheostomy tube for greater than or equal to 16 hours per day.

Effective price is for adults with SMA, the effective price for paediatric patients with SMA was proposed to continue to be \$██████.

Source: Tables 1.5 and 1.6, p48 and p50 of the resubmission.

3.2 The resubmission requested that the existing listing for nusinersen in symptomatic patients be updated (per the underlining and strikethrough in the restriction above) to include the proposed new populations i.e. to allow initiation and continuation in patients with symptom onset prior to 19 years of age, to allow use in patients with all forms of type III SMA, and to remove the age limit of 18 years for initiation of treatment.

- 3.3 The resubmission proposed a special pricing arrangement with a requested effective price of \$ [REDACTED] per dose, and proposed to rebate [REDACTED]. However, this price was only proposed for adult patients over 18 years of age initiating treatment on nusinersen. For non-adult patients with Type IIIb SMA, the existing listed price (\$ [REDACTED] per dose) was requested, with [REDACTED] rebated.
- 3.4 The requested restriction included a patient population for whom very little clinical evidence was provided: persons aged 18 years or younger initiating treatment with nusinersen who are not currently covered by the existing symptomatic listing for nusinersen (i.e. patients with Type IIIb SMA, where onset of symptoms commence at or after 3 years of age). While a small number of patients in the presented studies were aged 16 to 18 years, no data were presented for patients with Type IIIb SMA who were aged younger than this at the time of initiation of nusinersen.
- 3.5 As a minimum, the resubmission requested removing the age restriction for initiation of treatment with nusinersen i.e. allowing initiation in patients >18 years with SMA symptom onset prior to 3 years of age (Type I, II or IIIa). The resubmission stated that a cut-off age for initiation of treatment is not equitable because patients with the exact same clinical features born one day apart would have different access to treatment on the basis of their day of birth. The ESC considered that, rather than removing criteria around age, alternative criteria could be considered that identify patients most likely to benefit (e.g. based on level or type of disability). Specialist clinical input would be required to help determine such criteria and thus define the appropriate patient population.
- 3.6 The resubmission proposed that the existing ‘stopping rule’ should apply, i.e. “treatment must be ceased when invasive permanent assisted ventilation is required in the absence of a potentially reversible cause while being treated with this drug”. The resubmission also proposed the addition of a further criterion: “or when further treatment is deemed futile”, which it stated was based on expert opinion. This would allow patients to continue nusinersen if they experience a decline in motor function. This was inconsistent with the economic model, which assumed that the effectiveness of nusinersen would remain constant for patients who remain on treatment. A stopping rule / continuation criteria may be required given that 3.5% to 13% of patients may still experience a decline in motor function, upper limb strength or in distance walked in the six-minute walk test (6MWT) despite being treated with nusinersen. The Pre-Sub-Committee Response (PSCR agreed it would be appropriate to include continuation criteria for adult SMA patients and suggested that patients could be required to cease treatment if they experience: ‘objectively assessable, SMA-related deterioration in motor function with validated scales’ as proposed in Hagenacker 2019 (Hagenacker 2019 also added that ‘a delay in progression, however, may justify further treatment’). The PSCR stated that such a criterion would require patients to cease nusinersen if they are not benefitting from treatment, without being ‘limited to a single scale that may not be applicable to all patients in all circumstances’. However the ESC considered that the PSCR’s proposed stopping rule was subjective

and that ‘validated scales’ and ‘objectively assessable’ may require further definition. Specialist clinical input may be required to define an appropriate stopping rule/continuation criteria for the requested population.

- 3.7 The ESC noted that the existing listing requires the patient to be treated by, or in consultation with, a specialist medical practitioner associated with a neuromuscular clinic of one of eight recognised hospitals in the management of SMA. The ESC considered that it was unclear whether adult clinical management providers and services would be within the same context. Specialist clinical input may be required to help determine the appropriate prescriber/treatment setting for adult patients. SMA Australia conducted a survey of 113 adults with SMA (refer to ‘consumer comments’), which found that 61% of those surveyed hadn’t seen a neurologist in ‘years’ or weren’t connected with a neurologist at all. The pre-PBAC response stated that ‘neuromuscular centres of excellence do not currently exist to serve the adult SMA population’ and ‘the SMA clinical community is currently working to identify the appropriate treatment setting for adult patients’, with the latter outlined by the clinician who presented at the hearing (refer to ‘sponsor hearing’).
- 3.8 The requested listing requires the condition to be ‘5q homozygous deletion, mutation of, or compound heterozygous mutation in the SMN1 gene of type I, II or III’. The ESC noted that adult patients with SMA may have had genetic testing performed some time prior to commencing PBS-subsidised nusinersen. The ESC considered that it was unclear whether clinicians would have confirmatory records of such testing, noting that the cost of a test for deletion or mutation in the SMN1 gene is not funded by the MBS and patients will generally rely on public hospital systems to cover the costs of such testing. The pre-PBAC response stated that the sponsor [REDACTED]
- 3.9 The ESC considered it may be appropriate to include a clinical criterion which states that nusinersen must not be used in combination with, or in patients who have previously received treatment with, onasemnogene abeparvovec, risdiplam, or branaplam (refer to ‘Other relevant factors’ section). Specialist clinical input may be required.
- 3.10 The number of repeats requested for continuing treatment (two) is higher than the number of repeats for the current continuing treatment listing (zero). No rationale was provided, and the PBAC considered the increased number of repeats did not seem reasonable.
- 3.11 The existing listing for symptomatic patients outlines the defined signs and symptoms for patients with Types I, II and IIIa SMA (of which a patient must have experienced at least two, prior to the cut-off age). Defined signs and symptoms for the broader Type III population (including IIIb and IIIc) will need to be detailed in the restriction. Specialist clinical input may be required.

3.12 While the requested listing comprised an update to the existing listing, the resubmission requested a separate PBS item number for the initial treatment of adult patients to facilitate [REDACTED]

[REDACTED]. This would not be possible with the proposed combined listing for the new and existing patient populations, and instead would require two separate initiation restrictions (one for patients aged > 18 years and one for patients aged ≤ 18 years) and potentially two separate continuing restrictions.

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

4 Population and disease

4.1 SMA is an autosomal recessive progressive neuromuscular disease 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 correlates to earlier age of onset and increased disease severity. As outlined in Table 3, 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). The resubmission has not requested a listing for patients with Type IV SMA, defined as age at symptom onset of more than 18 years (i.e. at 19 years of age or more).

Table 3: Classification of SMA based on age of symptom onset and maximal motor function achieved

Terminology	SMA Type	Age at symptom onset	Highest motor function achieved	Average life expectancy
Pre-natal	0	Prenatal	None – unable to sit or roll	Death within weeks
Infantile-onset	I	< 6 months	Unable to sit or roll	Death within 2 years
Childhood-onset	II	6 - 18 months	Sitting – unable to walk independently	Survival into adulthood
	III	< 3 years (IIIa) > 3 years (IIIb) > 12 to ≤18 years (IIIc)	Independently stand and walk, may lose ability to walk over time	Normal lifespan
Adult-onset	IV	> 18 years	Normal – mild motor impairment.	Normal lifespan

Source: Table 1.1, p29 of the submission.

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

5 Comparator

5.1 The resubmission nominated placebo/standard of care as the main comparator.

5.2 There are two near market comparators - onasemnogene abeparvovec (Zolgensma) gene therapy and risdiplam, an orally administered SMN2 splicing modifier.

Onasemnogene abeparvovec (Zolgensma) is approved in the US and received conditional approval by the European Medicines Agency in May 2020, but is not currently registered in Australia. A submission for onasemnogene abeparvovec (Zolgensma) is being considered at the November 2020 PBAC meeting for paediatric patients less than 2 years of age with Type I SMA. Risdiplam was registered by the FDA on 7 August 2020 for the treatment of SMA in patients 2 months of age and older.

- 5.3 In addition, while sodium valproate is not approved for the treatment of SMA in Australia, that there is some evidence (Elshafay et al, 2019¹) to show that it may improve gross motor function in patients with SMA. Similarly, salbutamol (while not approved for the treatment of SMA in Australia) is often used in some countries in clinical practice, based on functional improvements seen in open label studies in children. In a study identified during the evaluation by Sivo et al, 2015² in 74 non-ambulant patients with SMA, 100% of patients were taking salbutamol. The publication stated that it was the author's experience that the effect reaches its peak at 6 months after administration, with further minimal improvement between 6 and 12 months.

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

6 Consideration of the evidence

Sponsor hearing

- 6.1 The sponsor requested a hearing for this item. The clinician outlined that earlier treatment is associated with better outcomes. The clinician discussed the natural history of SMA in adults and the clinical studies of nusinersen in adults (Maggi and Hagenacker). The clinician outlined that functions that impact quality of life include ability to transfer, feed, wash, use the restroom and get dressed on their own and use of technological devices.
- 6.2 The clinician outlined that a group of 13 neuromuscular specialists who treat adult patients with SMA, representing major centres in Australia across every State and Territory, have convened. The group is developing consensus guidelines for the treatment of adults with SMA, along with a consensus on the minimum clinical and functional assessments, including collecting data through a patient registry. In terms of feasibility, the clinician stated that a neurologist is available in each state to administer nusinersen to adult patients.

Consumer comments

¹ Elshafay A, et al 2019. Efficacy and safety of valproic acid for spinal muscular atrophy: A systematic review and meta-analysis. *CNS Drugs* 33(3): 239-250.

² Sivo et al, 2015. Upper limb module in non-ambulant patients with spinal muscular atrophy: 12 month changes. *Neuromuscular disorders* 25: 212-215.

- 6.3 The PBAC noted and welcomed the input from individuals (121), health care professionals (6) and organisations (4) via the Consumer Comments facility on the PBS website.
- 6.4 The comments highlighted that stopping motor function deterioration was important as even minor deterioration can have significant impacts on patient quality of life. Patients described the progressive deterioration in activities of daily life, and the importance of at least maintaining their current functions particularly the ability to self-care (e.g. ability to feed and dress) and the ability to maintain independence and remain in the workforce. In addition to loss of motor function, patients described other impacts of the condition including nerve pain, breathing issues (including difficulty breathing and requiring ventilation), fatigue and mental health impacts. Patients described the fear of disease progression, in particular fears regarding the loss of independence and dignity. Patients also described the equity issues with the existing age cut-offs.
- 6.5 SMA Australia conducted a survey of 113 adults with SMA, which found that 93% of respondents want access to treatment and that there was a preference for oral treatment. The survey included the values and perspectives of adults with SMA. Key concerns included the decline in everyday living skills and independence, the decline in function, fatigue, the impact on mental health, and the flow-on effects to extended family.
- 6.6 Clinicians outlined that it can be difficult to assess the impact of treatment using functional motor scales, and that patient reported outcome measures may be more reflective of the small physical changes that lead to maintenance of current levels of function.

Clinical studies

- 6.7 The resubmission was based on two studies of nusinersen in patients aged 16 years or more with SMA Type II or III disease (Hagenacker 2020 and Walter 2019). Natural history data from four studies (Montes 2018, Pera 2019, Wadman 2018 and Mercuri 2016) was also presented from which the resubmission provided a naïve indirect comparison of outcomes compared to patients treated with nusinersen from the Hagenacker 2020 study only. The evaluation considered that the exclusion of the Walter 2019 study from the indirect comparison was unreasonable. Reasons for exclusion of Walter 2019 from the indirect comparison given by the resubmission appeared to be invalid in that baseline data were available to enable calculation of change from baseline for the outcomes presented in the publication. The PSCR maintained that it was appropriate to exclude the Walter 2019 study from the naïve comparison since attrition observed at assessments after baseline meant that the baseline values were no longer applicable and the change from baseline could not be adequately determined. However, the ESC noted that 2 of 19 patients withdrew during the Walter 2019 study and considered that the change from baseline could be adequately assessed.

- 6.8 The resubmission also excluded a number of studies that included patients treated with nusinersen, based on either the study having low patient numbers, or the study having only limited baseline and outcome data. However, it was not considered reasonable for the resubmission to have excluded these studies given the limited amount and quality of the evidence available for nusinersen. Brief outcome data for nusinersen treated patients from these studies (Yeo 2020³, Jochmann 2020⁴ and Veerapandiyan 2019⁵) were also summarised during the evaluation where it was available.
- 6.9 From the search for natural history data, the resubmission also excluded studies by Mazzone 2013⁶ and Bonati 2017⁷. While the resubmission argued that these studies had low patient numbers, both of these studies were considered relevant and results were also summarised during the evaluation.
- 6.10 Only data from the Hagenacker 2020 study were used in the economic evaluation.
- 6.11 Apart from the small number of patients aged 16 to 18 years in the Hagenacker 2020 study (approximately 5 patients at the 14-month assessment point), and any patients aged 18 years in the Walter 2019 study, the resubmission provided no clinical evidence of the efficacy or safety of initiating treatment with nusinersen in patients aged 18 years or less. The PSCR argued that, in the absence of data in patients aged 18 years or less with Type IIIb SMA, the benefit could be inferred as it would likely be the same or greater than that observed in adults with Type IIIb SMA as ‘these patients are earlier in the course of the disease and would therefore be able to maintain greater function over their lifetime’. However, the ESC noted that the resubmission proposed [REDACTED] in patients aged 18 years or less with Type IIIb SMA.
- 6.12 Details of the studies presented in the resubmission are provided in Table 4.

³ Yeo C, et al 2020. Prospective Cohort Study of Nusinersen Treatment in Adults with Spinal Muscular Atrophy. *Journal of Neuromuscular Diseases*, 7(3), pp.257-268.

⁴ Jochmann E, et al 2020. Experiences from treating seven adult 5q spinal muscular atrophy patients with Nusinersen. *Therapeutic Advances in Neurological Disorders*, 13, p.175628642090780.

⁵ Veerapandiyan A, et al 2019. Nusinersen for older patients with spinal muscular atrophy: A real-world clinical setting experience. *Muscle & Nerve*, 61(2), pp.222-226.

⁶ Mazzone E, et al 2013. Six minute walk test in type III spinal muscular atrophy: A 12 month longitudinal study. *Neuromuscular Disorders*, 23(8), pp.624-628.

⁷ Bonati U, et al 2017. Longitudinal characterization of biomarkers for spinal muscular atrophy. *Annals of Clinical and Translational Neurology*, 4(5), pp.292-304.

Table 4: Studies and associated reports presented in the resubmission

Study ID	Protocol title/ Publication title	Publication citation
Non-randomised studies		
Hagenacker 2020	Nusinersen in adults with 5q spinal muscular atrophy: a non-interventional, multicentre, observational cohort study.	The Lancet Neurology 2020. 19 (4), 317 - 325
Walter 2019	Safety and Treatment Effects of Nusinersen in Longstanding Adult 5q-SMA Type 3 - A Prospective Observational Study P.354 Treatment effects of nusinersen in longstanding adult 5q-SMA type 3 - a prospective observational study over 10 months	Journal of Neuromuscular Diseases 2019; 6: 453-465 Neuromuscular Disorders 2019. 29: S185
Data on the natural history of the disease in untreated patients		
Mercuri 2016	Patterns of disease progression in type 2 and 3 SMA: Implications for clinical trials	Neuromuscular Disorders 2016; 26(2): 126-131
Montes 2018	Ambulatory function in spinal muscular atrophy: Age-related patterns of progression	PLoS ONE 13(6): e0199657
Pera 2019	Revised upper limb module for spinal muscular atrophy: 12 month changes	Muscle and Nerve 2019; 59(4): 426-430
Wadman 2018	Muscle strength and motor function throughout life in a cross-sectional cohort of 180 patients with spinal muscular atrophy types 1c-4	European Journal of Neurology 2018; 25(3): 512-518
Study data planned for submission		
SMA Registry data	Characterization of patients with spinal muscular atrophy based on data of SMA registries	No data or publication citation was available

Source: Table 2.6, p74 of the resubmission and compiled during the evaluation from Section 2.2. of the resubmission.

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

Table 5: Key features of the included evidence

Study	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
Nusinersen						
Hagenacker 2020	57	Prospective, observational cohort study, single arm 14 months	High	Type II and III SMA	HFMSE, RULM, 6MWT	Discontinuation rate used, pro-rata 6MWT used but used inappropriately
Walter 2019	19	Prospective, observational, single-arm, 10 months	High	Type III SMA	HFMSE, RULM	Not used
Natural history data						
Mercuri 2016	268	Natural history data	Not assessed	Type II and III SMA	HFMSE	Not used
Montes 2018	73		Not assessed	Type II sitters to Type IIIb SMA	6MWT	Not used
Pera 2019	108		Not assessed	Type II to Type III SMA	RULM	Not used
Wadman 2018	180		Not assessed	Type IIa to Type IV SMA	HFMSE	Not used

Source: Compiled from Section 2 of the resubmission.

6.14 The studies were considered to have a high risk of bias, given that they were open label and non-comparative, non-randomised studies.

6.15 The resubmission stated that it intended to submit data from a planned analysis of three prospective, multi-centre, non-randomised registries that are designed to

collect longitudinal data on SMA patients irrespective of the treatment received. These comprise (i) SMARtCARE registry (50 neuromuscular centres across Germany, Austria, Switzerland, and anticipated to enrol 1,000 patients in the first year); (ii) International SMA Consortium Spinal Muscular Atrophy Patient Registry (ISMAR) (16 neuromuscular centres across USA, Italy, Great Britain, and has enrolled 1,041 patients); and (iii) CuidAME registry (6 neuromuscular centres across Spain, and has enrolled 54 patients). However, this information was not provided during the evaluation, PSCR or pre-PBAC response.

- 6.16 The resubmission compared the results for the Hammersmith Functional Motor Scale-Expanded (HFMSSE) from patients treated with nusinersen in the Hagenacker 2020 study to results from Mercuri 2016 for untreated patients, and to the results from the cross sectional study by Wadman 2018, where correlation of outcomes and age were used as a proxy for longitudinal change.
- 6.17 The HFMSSE assesses 33 functional motor tasks such as sitting, rolling, 4-point kneeling, crawling, transitioning from floor to sitting and sitting to standing, standing with support and assistance, walking with support and assistance and stair ascent and descent. Each item HFMSSE is allocated a score of 2, 1 or 0 according to pre-determined criteria (for a total score of 66). A score of 0 indicates inability to complete the task, a score of 1 meaning the task can be completed with compensation and a score of 2 meaning the task can be completed normally, without compensation.
- 6.18 The resubmission's comparison of HFMSSE outcomes was considered to have been hampered by differences between the study populations that were likely to have caused heterogeneity. This was not adequately addressed by the resubmission. In particular, as the rate of change in HFMSSE appeared to be dependent on a number of factors, including the type of SMA, whether the patient is ambulant/non-ambulant, and age of the patient (noted in Mercuri 2016 for non-ambulant patients), the indirect comparison was considered to be limited by the differences in regard to these variables between the nusinersen and natural history studies. For example, Mercuri 2016 included 17/30 (57%) patients with Type II SMA compared to 19/57 (33%) at the 14-month assessment point in Hagenacker 2020. Further, 25.4% of patients in Mercuri 2016 were ambulant compared to 37.7% in Hagenacker 2020 at the 14-month assessment point.
- 6.19 In the Wadman 2018 natural history study, a ceiling effect was observed for HFMSSE in patients with Type III SMA and a floor effect for SMA Types Ic and II, suggesting that the HFMSSE is not well able to detect small changes in functional abilities in patients with low or with high HFMSSE scores.
- 6.20 While the resubmission did not specifically define a minimum clinically important difference (MCID), it stated that a meaningful change in the HFMSSE was considered to be at least a 3-point change from baseline. In its consideration of nusinersen in March 2018, the PBAC considered "that mean improvement in HFMSSE score of 3.9 points in the nusinersen treatment arm of the CHERISH trial compared to a decline of -1.0

points in the sham-control arm may be clinically meaningful” (PBAC Public Summary Document (PSD), March 2018, para 5.13), and that a stable HFMSE score may also be meaningful to patients (PBAC PSD, March 2018, para 6.5).

- 6.21 The resubmission also compared the results for nusinersen treated patients in Hagenacker 2020 to those for untreated patients in Pera 2019 in relation to the Revised Upper Limb Module (RULM) test. The RULM test is an outcome measure specifically developed to assess upper limb functional abilities in SMA patients. The test assesses important aspects of upper limb function including the ability to drink from a cup, lift weighted items to and above shoulder level, drawing, opening containers, switching on lights and reaching and manipulation. Items are scored either 0, 1 or 2 as per the HFMSE. The total score ranges from 0 to 37 with higher scores indicating greater functional abilities. While an MCID for the RULM is yet to be determined in SMA, the resubmission stated that a +/- 2-point change has been previously considered clinically meaningful (Sivo 2015⁸).
- 6.22 The resubmission additionally compared the results for nusinersen treated patients in Hagenacker 2020 to those for untreated patients in Montes 2018 in relation to the six-minute walk test (6MWT). The 6MWT measures the distance in metres that a patient can walk in 6 minutes. The resubmission stated that a previously established MCID was 30 metres in patients with Duchenne Muscular Dystrophy, based on McDonald 2010.
- 6.23 The ESC considered that the importance of these outcomes (and the relevance of changes in these scores) in terms of clinically meaningful benefits for adult patients with SMA was unclear. The ESC considered that it was unclear which motor changes impact quality of life in adults and noted that consumer preferences tended to be around maintenance of upper limb function (e.g. for basic self-care, using devices, steering a wheel chair) and that, for many non-ambulant patients, mobility in terms of transfer movements in and out of chairs was clinically meaningful. The specialist who presented at the hearing stated that critical functions in adult patients include the ability to transfer, feed, wash, use the restroom and get dressed on their own, and indicated that some of the items measured on the HFMSE scale relate to these critical functions. The PBAC considered that specialist clinical input may be required to better understand the clinical significance of the outcomes in adults.
- 6.24 The pre-PBAC response stated that the main goal of treatment is stabilisation of disease and maintenance of motor function, and that a stable HFMSE score is also meaningful to patients.

⁸ Sivo S, et al 2015. Upper limb module in non-ambulant patients with spinal muscular atrophy: 12 month changes. *Neuromuscular disorders* 25: 212-215.

Comparative effectiveness

6.25 For the outcome of HFMSE, the results from Hagenacker 2020 are presented in Table 6.

Table 6: Change in HFMSE over the study period in Hagenacker 2020

HFMSE	6 months	10 months	14 months
N	124	92	57
Mean score (SD)	22.47 (22.41)	25.52 (22.97)	27.77 (23.47)
Mean difference vs baseline (95%CI)	1.73 (1.05 - 2.41)	2.58 (1.76 - 3.39)	3.12 (2.06–4.19)
P-value	<0.0001	<0.0001	<0.0001
Analysis of change			
≥3 point increase	35 (28.2%)	33 (35.9%)	23 (40.4%)
1-2 point change	22 (17.7%)	18 (19.6%)	16 (28.1%)
0 point change	53 (42.7%)	35 (38.0%)	16 (28.1%)
Negative change	14 (11.3%)	6 (6.5%)	2 (3.5%)

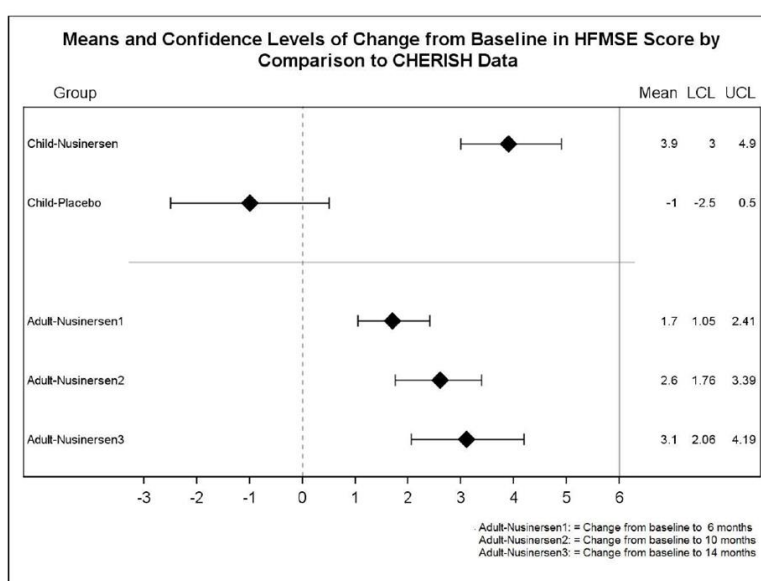
CI, confidence interval; HFMSE, Hammersmith Functional motor scale expanded; N, number; SD, standard deviation
Source: Table 2.26, p117 of the resubmission.

- 6.26 The resubmission stated that 40.4% of patients treated with nusinersen in Hagenacker 2020 demonstrated an improvement of 3 points or greater in the HFMSE at 14 months and the resubmission contrasted this to untreated patients in Mercuri 2016, where only 6.7% of patients achieved this outcome. An improvement of at least 3 points was more likely in patients with Type III SMA compared to those with Type II SMA for nusinersen treated patients (52.6% versus 15.8% respectively) in the Hagenacker 2020 study.
- 6.27 Overall, the mean change in HFMSE from baseline was 1.73 for patients included in the 6-month analysis, 2.58 for patients included in the 10-month analysis, and 3.12 for patients included in the 14-month analysis. These differences were statistically significant.
- 6.28 The pre-PBAC response stated that additional data were provided by the principal study investigator (Professor Hagenacker) which “indicated that of the 57 patients who had completed the 14 month follow up in the Hagenacker study, 27 continued to be on nusinersen treatment beyond 24 months of follow-up, with no evidence of demonstrated loss of treatment efficacy. Of these 27 patients, the vast majority (n=24, 89%) had achieved stabilisation or a clinically meaningful improvement in motor function defined as at least a 3 point increase in the HFMSE score. These data have not yet been analysed and therefore were not able to be provided for this response.”
- 6.29 Subgroup analyse reported in the Hagenacker 2020 study at 14 months showed that efficacy was higher for patients with a baseline HFMSE score of 35 or more (+4.6) compared to those a baseline score of less than 35 (+2.2). Similarly, there was a greater improvement from baseline to 15 months for patients with Type III SMA (+4.2: SD 4.5) compared to patients with Type II SMA (+1.1: SD 1.4). There were also significantly larger increases from baseline in the ambulant compared to the non-

ambulant subgroups at all three time points (+2.1 for non-ambulant patients compared to +4.6 for ambulant patients, $p=0.0127$ at 14 months).

- 6.30 It was noted during the evaluation, that the Hagenacker 2020 publication stated that as there were higher baseline values in patients who had completed the 14-month follow-up visit compared to those who started treatment later (only having their data analysed at 6 or 10 months) that it could not be ruled out that the patients who started the earliest on nusinersen in this study were those clinically less severely affected, given that some centres preferred to start treatment in patients less severely affected first because of technical aspects of the injection procedure. It is therefore possible that the efficacy of nusinersen at the 14-month assessment point will be lower than reported in the publication once all patients treated reach that assessment point.
- 6.31 The resubmission contrasted the results for change in HFMSE in Hagenacker 2020 to those seen in the CHERISH trial (which compared nusinersen to sham-control/placebo in patients with childhood-onset SMA (Type II)), which was presented in the November 2017 PBAC submission (Figure 1).

Figure 1: Means with 95% confidence intervals of HFMSE difference in Hagenacker 2020 from baseline to 6, 10 and 14 months (labelled as Adult-Nusinersen1, 2 and 3, respectively) by comparison to CHERISH data (Child – Nusinersen and Placebo)



Source: Figure 2.6, p122 of the resubmission.

- 6.32 While the resubmission inferred that the benefit of nusinersen in adult patients was comparable to that seen in children in the CHERISH trial, the evaluation noted that the patients in the CHERISH trial had Type II SMA, and that for the Type II SMA patients in Hagenacker 2020, the mean change in HFMSE from baseline was only 1.1 points at 14 months (even lower at 0.6 points at the 6 month analysis and 0.8 points at the 10 month analysis), which was substantially lower than that seen in the CHERISH trial. Further, as the greatest benefit of nusinersen may have been apparent in the 14-month analysis (given as discussed above, the possibility that less severely affected

patients were enrolled in the study first), it is likely that the benefit of nusinersen would lie somewhere in between the benefit observed at the 6-month and 14-month analyses.

- 6.33 The annualised change from baseline in HFMSE across the Hagenacker 2020 and Mercuri 2016 studies, by SMA Type, is summarised in Table 7.

Table 7: HFMSE change from baseline across studies

Study	Type	N	Age (years)	Baseline HFMSE	Annualised change from baseline
Nusinersen studies					
Hagenacker 2020	All	57	33 at start	24.65	+3.12 (4.02: 2.06 to 4.19) ^a
	Type II	19	28.9 at start	4.8	+1.1 (1.4; 0.4 to 1.7) ^a
	Type III	38	35.7 at start	34.6	+4.2 (4.5; 2.7 to 5.7) ^a
Walter 2019	Type III (All)	19	25.1 at start	35.2	+4.34 ^c
Natural history studies					
Mercuri 2016	Type II	17	17.97 plus	4.84	-0.059 ^b
	Type IIIa	3	18 plus	55.2	-0.66 ^b
	Type IIIb	9	18 plus		0 ^b

^a Data from Hagenacker 2020 represents 14 month assessment expressed as mean difference (SD; 95% CI)

^b Recalculated during the evaluation from -0.40 to 0 after excluding one patients aged 17.64 years.

^c At 10 months

Source: Table 2.41, p138 of the resubmission, and Hagenacker 2020.

- 6.34 The resubmission chose to exclude the Walter 2019 study from its naïve indirect comparison (as outlined in paragraph 6.1). Patients in the Walter 2019 study experienced an increase in HFMSE over the 10 month duration of the study, however the difference from baseline of 4.34 points was not statistically significant ($p=0.201$). The study reported that based on data from the last visit, 41% of patients reported an improvement, 23.5% of patients remained stable and 23.5% of patients reported a decline in HFMSE. Five of 17 patients (29.4%) reported a change in the HFMSE of more than 3 points. While patient numbers in the Walter 2019 study were lower at only 19 patients compared to Hagenacker (139 enrolled patients and 57 patients who completed the 14-month assessment), this in and of itself was not considered a reason to exclude the study from the indirect analysis. It was not apparent why the study resubmission's naïve indirect comparison did not include this study.
- 6.35 Overall, the data on HFMSE from single arm, non-comparative, non-randomised studies of nusinersen suggested that there may be an increase of 1.1 to 4.2 points over 14 months for adult patients with Type II or III SMA initiated on nusinersen, noting that a small proportion of patients may also display motor function decline (e.g. 11.3%, 6.5% and 3.5% of patients in Hagenacker 2020 at the 6, 10 and 14 months analysis respectively, and 23.5% of patients in Walter 2019 at 10 months).
- 6.36 Untreated adult patients in Mercuri 2016 in contrast, displayed a change in HFMSE over 12 months of 0 in patients with Type IIIb SMA, -0.66 for Type IIIa and -0.059 for Type II SMA. While the resubmission also contrasted the results to those from Wadman 2018, where there was stated to be a decline in motor function per year of

between 0.03 to 1.64 points, these values could not be accurately calculated from data in the publication given the way age cohorts were used in the study and how the data were reported. The Wadman 2018 study was further limited in that it simply reported average HFMSE for patients in various age cohorts at a set point in time, and not changes in the same patients over time.

6.37 For the outcome of RULM, the change from baseline is shown in Table 8.

Table 8: RULM change from baseline across studies

Study	Type	N	Baseline RULM	Change from baseline
Nusinersen studies				
Hagenacker 2020	All	57	23.8 (12.2)	+1.09 (1.75)^a
	Type II	19	12.3 (9.0)	+1.6 (2.0; 0.7 to 2.5) (p=0.0049)
	Type III	38	29.5 (9.1)	+0.7 (1.7; 0.2 to 1.3) (p=0.0100)
Walter 2019	Type III (all)	19	32.32 (7.3(9)	+0.74 (p=0.048)^c
Natural history studies				
Pera 2019 Patients ≥18 years ^b	All	24	22.0 (11.76)	-0.7 (2.5)
	Type II	11	11.8 (5.87)	+0.6 (1.9)
	Type III non-ambulant	6	22.7 (7.69)	-1.7 (2.4)
	Type III ambulant	7	36.0 (1.91)	-1.4 (2.7)

^a Data presented from Hagenacker 2020 are based on the 14-month assessment and presented as mean difference (SD; 95% CI); data presented from Pera 2019 are 12-month changes, expressed as mean (SD).

^b Data extracted using DigitizeIT Software. Data and subsequent calculations are presented in 'Natural history_data extraction.xls' (Attachment 2)

^c Values at 10 months

Bold values are statistically significant

Source: Table 2.42, p141 of the resubmission and Hagenacker 2020.

6.38 Across Types II and III SMA, there was a mean change of 0.59 at 10 months and 1.09 at 14 months in the RULM in Hagenacker 2020. The resubmission noted that there was a ceiling effect, with 28 (23%) patients having a maximum RULM score at baseline. Of these patients, all maintained full functionality after 6 months of treatment and showed no evidence of decline.

6.39 In relation to the MCID, the resubmission stated that the proportion of patients aged 18 years or more with a clinically meaningful decline in the RULM (a 2 or more point change) was greater in the Pera 2019 study compared with nusinersen treated SMA patients (27.3% vs 3.4%) aged 16 years or more in Hagenacker 2020, while the proportion of patients demonstrating a clinically meaningful improvement in upper limb function was substantially higher in the nusinersen study compared with untreated adult patients in Pera 2019 (36.2% vs 9.1%).

6.40 The resubmission chose to exclude the results for RULM reported in the Walter 2019 study from its naïve indirect comparison (as outlined in Paragraph 6.1). It was noted that the Walter 2019 study reported a small increase in RULM from baseline to 10 months of 0.74 (32.32 to 33.06 (p=0.048)) for nusinersen treated patients, which was similar to the change at 10 months in Hagenacker 2020. There were 2/17 (11.8%) of patients included in the Walter 2019 study who showed a decline in relation to RULM. Both patients were non-ambulant at entry to the study.

- 6.41 In relation to 6MWT, the resubmission stated that there was a change of 46 metres for ambulant patients in Hagenacker 2020 at 14 months, and this was compared to a decline of 9.7 metres in natural history patients as reported by Montes 2018 at 12 months. Similar to results for HFMSE and RULM, some nusinersen treated patients reported a decline in the 6MWT in Hagenacker 2020, with 3 of 25 patients (12%) reporting a negative change at 14 months. Based on this comparison, and the previously established MCID of 30 metres in patients with Duchenne Muscular Dystrophy, the resubmission asserted that 60% of ambulant patients achieved this outcome in Hagenacker 2020.
- 6.42 The resubmission chose to exclude the results from the Walter 2019 study in relation to 6MWT in its naïve indirect comparison. Walter 2019 reported an increase in distance walked at 10 months of 8.25 metres for ambulant nusinersen treated patients. Two of 25 patients reported a decline in 6MWT of 7 metres and 14 metres. It was not apparent why these results were excluded from the resubmission's naïve indirect comparison.
- 6.43 Other natural history studies identified during the evaluation reported conflicting results for the 6MWT for untreated patients with SMA compared to the results used in the resubmission's naïve indirect comparison from Montes 2018. These results were:
- An increase of 17.86 metres after 12 months was reported by Mazzone 2013 for Type IIIb SMA patients and a decrease of 5.97 metres for Type IIIa SMA patients, and while these results also included non-adult patients, it was not apparent from the study that adult patients overall experienced a decline in HFMSE.
 - An average increase in distance walked in the 6MWT of 38.9 metres after 12 months in a study by Bonati 2017 in 18 ambulant patients with an average age of 32 years.
- 6.44 Despite these varying results, the resubmission chose to use the value of a 46 metre increase from Hagenacker 2020 in the economic evaluation, inappropriately attributing this increase to all patients (not just ambulant patients). The previous November 2017 submission suggested that there would be an annual decline of 1.46 metres for Type III SMA ambulant untreated patients compared to an increase of 21 metres at year 1 relative to baseline for patients treated with nusinersen in the CS12 study.
- 6.45 The PSCR provided additional data from Maggi 2020, which was a recently published retrospective cohort study of 116 Italian patients with SMA Type II or III who initiated nusinersen in adulthood (>18 years of age). The median age at first administration was 34 years (range 18–72). Maggi 2020 found a mean (SD) increase of 1.2 (± 2.68) and 2.85 (± 2.93) points in HFMSE among patients with SMA II (n=5, p = not significant) and SMA III (n=46; p<0.0001) patients, respectively at 14 months post-baseline. Ambulant patients demonstrated a significant mean (SD) improvement in the 6MWT of 23.11 (51.2; p=0.016) metres at 14 months post-baseline. The magnitude of clinical

improvement in patients with Type III SMA was lower than that reported in Hagenacker 2020 (HFMSE: mean increase of 2.85 versus 4.2 reported in Maggi 2020 and Hagenacker 2020, respectively; 6MWT: mean increase of 23.11m versus 46m). The authors stated this may have been due to the Maggi 2020 study recruiting patients with worse motor performance at baseline (baseline 6MWT 308.5m versus 321.8m). The pre-PBAC response noted that the proportion of patients who achieved a clinically meaningful improvement of ≥ 3 points HFMSE was 40% in Hagenacker 2020 and 49% in Maggi 2020 at 14 months.

- 6.46 The resubmission did not consider comparative efficacy in patients aged 18 years or less who developed symptoms of SMA at 3 years or age or later (with Type IIIb SMA), and as such it was not possible to conclude anything about the comparative efficacy (or safety) of nusinersen in this patient population.

Comparative harms

- 6.47 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).
- 6.48 Adverse events occurred in 82 patients (47%) throughout the 14-month follow-up period in Hagenacker 2020. The most commonly reported adverse reactions comprised headache (20%), back pain (9%) and nausea (7%), all considered to be related to the lumbar puncture procedure. Two patients withdrew from the treatment because of adverse drug reactions and no deaths occurred during the study period.
- 6.49 In the Walter 2019 study, post-lumbar puncture headache was reported in 4/19 (21%) of patients in a total of 11 of 108 lumbar punctures (10%). No patients discontinued treatment as a result of procedure or treatment related adverse events.
- 6.50 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.
- 6.51 The Maggi 2020 study, provided in the PSCR, found that post-procedure headache was observed at least once in 43/116 (37.1%) patients. Headaches were orthostatic, mild to moderate in intensity and spontaneously resolved in a few days, except for five patients who required hospitalisation. Lumbar pain was reported in 10/116 (8.6%) patients.

Benefits/harms

- 6.52 The naïve indirect comparison presented in the resubmission did not allow for a quantitative comparison of the benefits and harms of treatment with nusinersen and standard of care in the requested patient populations. Accordingly, a benefits/harms table was not presented.

Clinical claim

- 6.53 The resubmission described nusinersen, for the treatment of adult patients with SMA, as superior in terms of effectiveness compared with standard of care and non-inferior in terms of safety. A claim was not made for non-adult patients with SMA who had the first onset of symptoms from 3 years of age or more.
- 6.54 The evaluation and the ESC considered that the magnitude and durability of benefit claimed in the submission were not adequately supported by the evidence presented due to:
- The lack of long-term data, with outcomes reported for the nusinersen treated patients only being up to 14 months. As such, the ESC considered that the durability of response with nusinersen in adults with SMA was uncertain.
 - The possibility of a placebo effect could not be ruled out for any of the efficacy outcomes.
 - The lack of randomised comparative data or statistical analyses for the indirect naïve comparisons presented.
 - The resubmission was selective in its choice of data for the comparisons with other studies reporting varying results.
 - The comparison for HFMSE in particular, was considered to have been limited by differences between the studies with respect to the type of SMA, the proportion of ambulant patients, and the age of the patients. The comparison may also have been limited by the different time periods for assessment of the outcome in terms of months of treatment/follow-up, which differed between the studies.
- 6.55 Further, the ESC considered that the incremental benefit of nusinersen in the requested population was unclear given the unknown impact of variables such as ambulant / non ambulant status, age of patient and rate of decline across types of SMA. The ESC reiterated the PBAC's previous concerns that overall it was 'uncertain of the extent and durability of benefit of treatment with nusinersen in the overall SMA population based on the evidence presented in the submission' (Nusinersen PSD, PBAC meeting November 2017, para 7.16).
- 6.56 In relation to safety, the PBAC previously considered (paragraph 11.4, nusinersen, Addendum to the July 2019 PSD November 2019) 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 patients). Adverse events associated with lumbar puncture administrations were also apparent in the clinical evidence presented in the resubmission and the resubmission made no attempt to demonstrate non-inferiority. Overall, the evaluation and the ESC considered that the claim of non-inferior safety compared to standard of care was not supported.
- 6.57 The PBAC considered that, while the claim of superior comparative effectiveness was reasonable, the magnitude and durability of benefit was not able to be quantified based on the data presented.

6.58 The PBAC considered that the claim of non-inferior comparative safety was not adequately supported by the data.

Economic analysis

6.59 The resubmission presented a cost-utility analysis. A cost-utility analysis was not presented in the previous submission considered by the PBAC in November 2017 for the requested patient populations: rather, a cost per responder analysis based on a 15 month duration for Type II SMA patients and approximately 2 years for Type III SMA patients, with an assumption of continued duration of response for nusinersen, was presented. Table 9 provides a summary of the model structure, key inputs and rationale.

6.60 As for the previous submission, no data from any of the studies presented in the comparative effectiveness section were used in the economic evaluation.

Table 9: Summary of model structure, key inputs and rationale

Component	Summary
Treatments	Nusinersen and continuation of standard of care versus standard of care alone
Time horizon	A lifetime horizon in the model base case versus 14 months in the Hagenacker 2020 study. The lifetime time horizon increased the uncertainty given the limited duration of available clinical data and the issues with the extrapolation outlined below.
Outcomes	QALYs
Methods to generate results	Markov model
Health states	Walking/standing: unaided –starting state assumed 18.5% of patients in this health state Walking/standing: aided – starting state assumed 18.5% of patients in this health state Non-ambulatory: able to sit – starting state assumed 63% of patients in this health state Non-ambulatory: unable to sit – starting state assumed 0% of patients in this health state Separate health states were used for on treatment and off treatment Dead – starting state assumed 0% of patients in this health state
Cycle length	4 months
Transition probabilities	For untreated patients, a rate of progression between health states of 2.3% per annum was assumed, derived from Zerres 1997 ⁹ . However the evaluation and ESC considered that the resubmission’s approach was flawed as the calculations assumed the patient’s age was reported on the horizontal axis of the Kaplan-Meier data, while the data actually reported the duration of disease since onset of symptoms. Adjusting for this, the evaluation calculated the loss of ambulation to be: 1.46% per year for Type IIIb SMA adult patients; 0.41% for patients aged 10-15 years at symptom onset; 1.1% for patients aged 6-10 years at symptom onset; and 1.43% for patients aged 3-6 years at symptom onset (rather than the 2.3% used in the resubmission). During evaluation, an alternative transition probability of 1% was tested in the sensitivity analysis for movement in the alive health states. The evaluation considered this was a reasonable proxy for a lower rate given that the aforementioned rates of loss of ambulation. Mortality was assumed to be the same for nusinersen and standard of care patients and this was considered to be reasonable. The resubmission assumed that patients treated with nusinersen would not decline into a less functional alive health state, which the evaluation and ESC considered was unreasonable since data presented from Hagenacker 2020 and Walter 2019 indicated that some nusinersen treated patients experience a decline in motor function.

⁹ Zerres K, et al 1997. A collaborative study on the natural history of childhood and juvenile onset proximal spinal muscular atrophy (type II and III SMA): 569 patients. *Journal of the Neurological Sciences*, 146(1), pp.67-72.

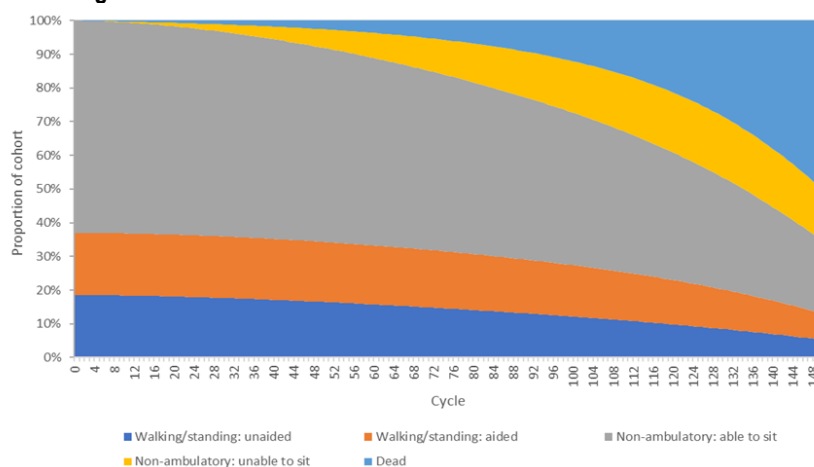
Component	Summary
Extrapolation method	<p>No extrapolation method was provided. The resubmission assumed the benefit of nusinersen would continue for patients remaining on treatment, indefinitely (i.e. patients on nusinersen were assumed to remain in the same health state unless they discontinued treatment or died). This assumption was not justified.</p> <p>For standard of care treated patients, the movement between health states was defined by the transition probabilities (see above), with a constant rate of decline predicted over time. The transition probabilities were based on the proportion of patients from Zerres 1997 who moved from the 'walking/standing' health states (aided and unaided combined) to the 'non-ambulatory: able to sit of unable to sit' health states. However, the resubmission applied these rates to movement between all health states, which was unjustified given that data in the Wadman 2017 supplementary appendix showed that different rates of progression apply for loss of ability to stand and to sit compared to loss of ability walk. Further, data presented in the Wadman 2017 supplementary appendix also suggested that loss of motor function is not constant over time. Overall, the resubmission's assumptions were not adequately justified.</p>
Health related quality of life	<p>Literature based – based on publication funded by sponsor of Lloyd 2019.</p> <p>Walking/standing: unaided: 0.72 Walking/standing: aided: 0.39 Non-ambulatory: able to sit:-0.04 Non-ambulatory: unable to sit: -0.12</p> <p>The evaluation and ESC considered that these values were highly uncertain for a number of reasons (e.g. use of vignettes rather than observed data, small survey of proxy clinician completers, use of adult scoring algorithm for child-specific health states). Alternate values were tested in sensitivity analyses, based on values estimated by clinical experts as part of the NICE consideration for nusinersen¹⁰</p>
Patients	SMA Type II or III with patients aged over 18 years at treatment initiation
Other nusinersen related costs	<p>Costs for administration and adverse events were appropriately applied, however there was no allowance made for monitoring for renal toxicity or thrombocytopenia and there was no allowance made for the cost of an SMN1 gene test. The pre-PBAC response stated that [REDACTED].</p>
Disease state costs	<p>It was not apparent that the resubmission's application of disease state costs from Klug 2016 would be applicable to the nominated health states, particularly for the assumption that non-ambulatory: unable to sit patients would have the same health state costs as Type I SMA patients in Klug 2016</p>

Source: Compiled during the evaluation from Section 3 of the resubmission.

- 6.61 The model did not consider costs or outcomes for non-adult patients (18 years or less) who had symptoms develop at 3 years of age or more. The cost-effectiveness in this patient population was not presented and remains unknown.
- 6.62 The model traces over time for the health states as provided by the resubmission are presented in Figure 2 and Figure 3.

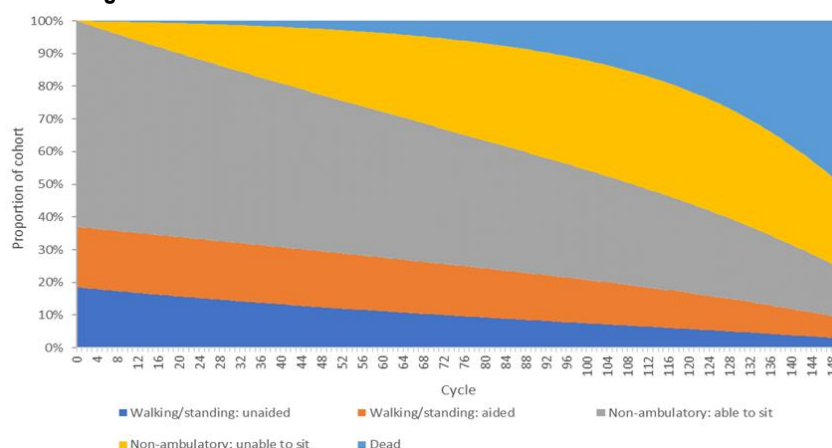
¹⁰ NICE: Nusinersen for treating spinal muscular atrophy. Technology appraisal guidance [TA588]. 24 July 2019: Available at: <https://www.nice.org.uk/guidance/ta588/evidence>

Figure 2: Health state changes over time: Nusinersen



Source: Figure 3.17, p203 of the resubmission.

Figure 3: Health state changes over time: Standard of care



Source: Figure 3.18, p203 of the resubmission.

- 6.63 The majority of the change in health states with the standard of care arm occurred due to movement of patients into the ‘unable to sit’ health state. This was because the model assumed that most (63%) patients would begin in the ‘non-ambulatory: able to sit’ health state. For nusinersen, the movement between health states was due to the assumed rate of discontinuation of 3.7% per year. The ICER generated by the model was highly dependent on the rate of movement between health states for standard of care patients and the assumed non-movement into lower health states for nusinersen treated patients who continue on treatment. Variations to these parameters resulted in substantial changes to the resubmission’s estimated ICER (see Table 11).
- 6.64 The model was dependent on a wide range of assumptions that could not be adequately validated during the evaluation. For example, none of the clinical evidence presented in the ‘comparative effectiveness’ section contained information on the proportion of patients treated with nusinersen who would move into a lower health

state over time, or patient derived utility values based on treatment with nusinersen, or actual costs for comparable patients treated with nusinersen versus standard of care. Further, the evaluation and the ESC considered that the model structure was limited in that it focused on changes based on gross motor function and it did not capture changes in fine motor function, which can be important to patients with SMA.

6.65 Key drivers of the model are presented in Table 10.

Table 10: Key drivers of the model

Description	Method/Value	Impact Base case: \$ [REDACTED] /QALY gained
Time horizon	A lifetime model was used in the base case, however use of shorter time horizons significantly increased the ICER, suggesting that any incremental benefit of nusinersen is dependent on continued use and the assumption of continued efficacy for patients remaining on treatment over the patient's lifetime, as well as the resubmission's assumed rate of progression for standard of care patients (see rate of progression for standard care below).	High, favours nusinersen Use of a 5-year time horizon increased the ICER to \$ [REDACTED] /QALY gained.
Rate of progression for standard care	A progression rate of 2.3% per annum based on the resubmission's calculation of weighted loss of ambulation in Zerres 1997. The evaluation, ESC and PBAC considered this rate was substantially overestimated.	High, favours nusinersen Use of a 1% rate of progression per annum increased the ICER to \$ [REDACTED] ¹
Extrapolation	The resubmission assumed that the treatment effect of nusinersen would not dissipate over time, and therefore that patients would only decline into a lower health state over time if they discontinued treatment. This assumption was not justified.	High, favours nusinersen This was difficult to test in a sensitivity analysis, however assuming a progression odds ratio of 0.25 (that patients on nusinersen progress at a quarter of the rate of standard of care patients), and assuming that only 50% of patients discontinue treatment after progression on nusinersen, the ICER increased to \$ [REDACTED] per QALY
Utility benefit for increase in 6MWT	The resubmission inappropriately applied a utility benefit for increased distance walked in the 6MWT to all patients, rather than to just patients who were already ambulant when they started nusinersen.	High, favours nusinersen Correction of this error increased the ICER to \$ [REDACTED] per QALY. The ESC considered this would be a more appropriate base case.
Utilities for health states	The evaluation, ESC and PBAC considered that the utility values for the model health states taken from Lloyd 2019 were highly uncertain.	High, unclear direction of bias Use of alternative utilities estimated by NICE clinical experts reduced the ICER to \$ [REDACTED] /QALY gained.

Source: Compiled during the evaluation from Section 3 of the resubmission and calculations undertaken during the evaluation.

The redacted values correspond to the following ranges:

¹>\$1,055,000/QALY gained

6.66 As for the November 2017 PBAC submission, the assumption that the treatment effect of nusinersen would not dissipate over time for patients remaining on treatment was a key driver of the model (as depicted in the time horizon and the extrapolation rows in Table 10 above). While the model included an allowance for patient discontinuation (based on a calculated rate of 3.7% at the 10 month time point from Hagenacker

2020), it was not clear that all patients treated with nusinersen who display disease progression would discontinue treatment. In the Hagenacker 2020 study at the 10-month time point for example, 6.5% of patients reported a worsening with respect to the HFMSE, and yet only 3.7% withdrew from treatment. In the Walter study after visit 4, only 2/19 patients withdrew their consent and stopped treatment (due to concerns regarding hydrocephalus development and planned pregnancy), however of the remaining patients, 5/17 reported disease worsening with respect to HFMSE by month 10 (23.5%).

- 6.67 The ESC considered that the utilities applied in the resubmission's model were not reliable. The utility estimates applied in the resubmission were from Lloyd 2019, which were based on proxy completion of the EQ-5D-Y (a youth version of the EQ-5D-3L) by five clinical experts using case vignettes. These were then valued using the adult EQ-5D-3L algorithm, and then applied to adults. The ESC acknowledged the difficulties associated with valuation of health in rare childhood conditions, but even in this context, considered the utility weights applied were not sufficiently reliable for decision-making purposes and were unlikely to capture the health-related quality of life of the requested patient population due to: the use of vignettes rather than observed data; the small survey of proxy clinician completers; and the use of the adult scoring algorithm for child-specific health states. The ESC also noted that the case vignettes described Type I and Type II SMA, and the utility weights applied were based on values derived predominantly for patients with Type II SMA. It was unclear if these values are applicable to patients with Type III SMA and/or to adult patients, where the resubmission expects the majority of the new use of nusinersen to be.
- 6.68 The ESC expressed a preference for utilities elicited from patient self-report data and considered that it would be more appropriate for the resubmission to have conducted a utility study in Australian patients with SMA who are relevant to the requested patient population.
- 6.69 Further, the resubmission did not allow for variation in utility values over time for patients in a given health state, and the values were based on changes in motor function rather than being broad enough to capture other benefits such as independence or the ability to self-care.
- 6.70 The resubmission assumed that there would be a gain in distance walked in the 6MWT for nusinersen-treated patients, and a utility benefit for this of 0.021 (based on data from Hagenacker 2020 and Shafrin 2017¹¹) The resubmission incorrectly applied this benefit to all patients treated with nusinersen, rather than to just ambulatory patients, which underestimated the ICER. The ESC considered that the base case

¹¹ Shafrin J, et al 2017. The association between observed mobility and quality of life in the near elderly. *PLOS ONE*, 12(8), p.e0182920.

should be revised to correct for this error. Further, it was not apparent that a utility benefit should apply for increased distance walked in the 6MWT.

6.71 The results of the resubmission’s stepped economic evaluation are presented in Table 11.

Table 11: Results of the stepped economic evaluation

Treatment arm	Nusinersen	Standard of care	Difference
Step 1: Trial-based cost per one point change in HFSME analysis - over 14 months			
Cost	\$ [REDACTED]	\$0	\$ [REDACTED]
Mean change in HFSME	3.12	0	3.12
Incremental cost per one point change in HFSME			\$ [REDACTED] ¹
Alternate step 1: Trial-based cost per responder (3 point or more increase in HFSME - over 14 months)			
Cost	\$ [REDACTED]	\$0	\$ [REDACTED]
Proportion of patients responding*	40.4%	6.7%	33.7%
Incremental cost per responder			\$ [REDACTED] ²
Step 2: Extrapolation of treatment costs: Modelled cost per one point change in HFSME analysis			
Cost	\$ [REDACTED]	\$0	\$ [REDACTED]
Mean change in HFSME	3.12	0	3.12
Incremental cost per one point change in HFSME			\$ [REDACTED] ³
Step 3: HFSME translated to QALYs: Modelled cost per QALY analysis			
Cost	\$ [REDACTED]	\$0	\$ [REDACTED]
QALYs	3.1209	2.1966	0.9243
Incremental cost per QALY			\$ [REDACTED] ⁴
Resubmission base case. Step 4: Incorporates SMA related health care costs: Modelled cost per QALY analysis			
Cost	\$ [REDACTED]	\$226,480	\$ [REDACTED]
QALYs	3.1209	2.1966	0.9243
Incremental cost per QALY			\$ [REDACTED] ⁴
Alternative base case: Apply utility gain for increase in distance walked to ambulatory patients only (correction of error)			
Incremental cost per QALY			\$ [REDACTED] ⁴

HFSME, Hammersmith Functional Motor Scale Extended; QALY, quality adjusted life year

* From Figure 2.6.1 of the commentary

Source: Table 3.39, p204 of the resubmission.

The redacted values correspond to the following ranges:

¹\$95,000 to <\$115,000/QALY gained

²\$855,000 to <\$95,000/QALY gained

³\$755,000 to <\$855,000/QALY gained

⁴>\$1,055,000/QALY gained

6.72 The resubmission’s base case incremental cost per QALY at approximately >\$1,055,000/QALY gained was extremely high. Given the utility gain for an increase in distance walked was incorrectly applied to all patients treated with nusinersen rather than to just ambulatory patients, the ESC considered the ICER of >\$1,055,000/QALY gained should be considered the base case ICER.

6.73 For context, in March 2018, the PBAC noted that the cost per QALY gained for patients with Type II/IIIa SMA was estimated to be an indicative ICER of \$255,000 to <\$355,000/QALY gained based on a health care perspective. The PBAC (in March 2018) considered that this ICER was considerably uncertain, and did not accept the proposed

price for all SMA types and advised that a price reduction accounting for utilisation in Type II/IIIa patients would be appropriate. The PBAC advised that a combination of reduction in price, increased rebates or lower financial caps would be necessary to achieve a cost-effective listing (Nusinersen PBAC PSD, March 2018, paragraphs 6.10 to 6.11).

- 6.74 The November 2017 submission requested consideration under the 'rule of rescue'. In November 2017, the PBAC did not consider the 'rule of rescue' criteria were met for SMA Type II. Further, the PBAC considered there was insufficient clinical data to ascertain whether the 'rule of rescue' criteria would be met for SMA Type III (5.11 Nusinersen PBAC PSD, November 2017, paragraphs 7.29 and 7.30).
- 6.75 An additional cost per responder analysis was included in the stepped economic evaluation during the evaluation. As shown in Table 11, the incremental cost per responder based on a 3 point or greater change on the HFMSE was estimated to be \$855,000 to <\$955,000/QALY gained (based on 14 month outcomes in Hagenacker 2020 (40.4%) versus Mercuri 2016 (6.7%)). This was calculated to allow some comparison to the cost per responder with Type II SMA in the first PBAC submission of \$ [REDACTED] (recalculated to be \$ [REDACTED] based on the current effective price of \$ [REDACTED] per vial rather than \$110,000 per vial in the first submission), noting that the current cost per responder is highly uncertain due to the lack of comparative data compared to the first submission where response rates of 56.8% versus 26.3% were seen for nusinersen and best supportive care treated patients respectively in the CHERISH trial (5.11 COM, November 2017 Table 2.8.3). The evaluation further noted that the ESC previously considered the nomination of a 3-point change as being clinically significant was poorly supported (Nusinersen PSD, November 2017 PBAC Meeting, para 6.52), and that the change from baseline to 14 months was lower for Type II patients than Type III patients in Hagenacker 2020 (1.1 versus 4.2), indicating that the proportion of Type II SMA patients achieving a 3-point or more increase in HFMSE would have been lower than the mean rates reported for all patients in this study.
- 6.76 Results of key univariate sensitivity analyses presented by the resubmission and undertaken during the evaluation are summarised in Table 12. These are based on the base case presented in the resubmission, and do not include the correction to apply the treatment utility benefit (for increase in distance walked) to ambulatory patients only.

Table 12: Key univariate sensitivity analysis: Incremental cost per QALY gained

	Incremental costs	Incremental QALYs	ICER (\$/QALY)
Base case (per resubmission)	\$ [REDACTED]	0.9243	\$ [REDACTED] ¹
Time horizon (base case: lifetime)			
1 year	\$ [REDACTED]	0.0222	\$ [REDACTED] ¹
5 years	\$ [REDACTED]	0.1288	\$ [REDACTED] ¹
Standard of care progression rate (base case: 2.3%)			
1%	\$ [REDACTED]	0.5610	\$ [REDACTED] ¹
Progression odds ratio, nusinersen versus standard of care (base case: 0, i.e. no progression on treatment)			
0.5 (progression rate = 1.2%)*	\$ [REDACTED]	0.9673	\$ [REDACTED] ¹
0.25 (progression rate = 0.6%)	\$ [REDACTED]	0.9958	\$ [REDACTED] ¹
0.25 progression odds ratio (progression rate = 0.6%), and only 50% of patients discontinuing after progression (base case 100%)	\$ [REDACTED]	0.7231	\$ [REDACTED] ¹
Health state utilities (base case walking/standing: unaided 0.72, walking/standing: aided 0.39, non-ambulatory: able to sit -0.04, non-ambulatory: unable to sit -0.12)			
'Non-ambulatory: unable to sit' = -0.04	\$ [REDACTED]	0.7484	\$ [REDACTED] ¹
'Walking/standing: unaided' = 0.5	\$ [REDACTED]	0.7941	\$ [REDACTED] ¹
'Non-ambulatory: able to sit' = 0.14	\$ [REDACTED]	1.1866	\$ [REDACTED] ¹
NICE utilities (walk/stand unaided = 0.85, walk/stand aided = 0.75, non-ambulatory: able to sit = 0.6, non-ambulatory, unable to sit = 0.25)	\$ [REDACTED]	1.1742	\$ [REDACTED] ¹
Treatment utility benefit – utility gain for increase in distance walked (base case 0.021)			
0	\$ [REDACTED]	0.6902	\$ [REDACTED] ¹
Apply treatment utility benefit of 0.021 to walk/stand unaided health state only	\$ [REDACTED]	0.7335	\$ [REDACTED] ¹

Values in italics were additional analyses conducted during the evaluation.

* Could not be replicated during the evaluation and appeared to be implausible.

** The ESC considered this should be the revised base case.

Source: Table 3.44, p211 of the resubmission and compiled during the evaluation.

The redacted values correspond to the following range

¹>\$1,055,000

6.77 The ESC considered that the ICER per QALY was underestimated, and the key uncertainties that had a large impact on the ICER were:

- the time horizon. A 1-year time horizon increased the ICER to over >\$1,055,000 per QALY gained, and a 5-year time horizon increased the ICER to over >\$1,055,000 per QALY gained. While the ESC did not believe that a time horizon below 5 years was reasonable, the current selection of base case time horizon was highly problematic given the uncertainty in the clinical data; and
- the rate of progression in the standard of care arm. If a rate of 1% was used, the ICER increased to >\$1,055,000 per QALY gained.

These were based on the resubmission's base case. Correcting the ICER by applying the treatment utility benefit (for increase in distance walked) to ambulatory patients only would further increase these ICERs.

Drug cost/adult patient initiated on nusinersen

Table 13: Drug cost per adult patient initiated on nusinersen (including cost of administration)

	Study dose and duration	Model	Financial estimates
Mean dose	4 loading doses and then doses every 4 months	4 loading doses (with one rebated) and then doses every 4 months	4 loading doses (with one rebated) and then doses every 4 months
Mean duration	14 months	Lifetime, with a 3.7% discontinuation rate per year (mean of 21.05 years and median of 17.5 years)	Lifetime, with no discontinuation per year in the base case
Cost/patient for loading doses over 2 months	(\$ [redacted] + \$424.33) x 4 = \$ [redacted]	(((\$ [redacted] + \$424.33) x 3) + \$424.33) = \$ [redacted]	(((\$ [redacted] + \$343.88) x 3) + \$343.88 = \$ [redacted]
Cost per 4-month cycle after the first cycle of 4 months	(\$ [redacted] + \$424.33) = \$ [redacted]	(\$ [redacted] + \$424.33) = \$ [redacted], less the cost for 3.7%/3 patients who discontinue each cycle = \$ [redacted]	(\$ [redacted] + \$343.88) = \$ [redacted]

Source: Calculated during the evaluation, where 3.7% is the assumed discontinuation rate for nusinersen per year. The financial estimates include the cost of administration with an 80% rebate (\$402.25 x 80%) and the cost of adverse events (\$22.08), while the economic model does not include the 80% rebate.

6.78 After the loading doses for the first 2 months, the cost per 4 month cycle for adult patients aged 19 years or more on initiation of nusinersen was estimated to be \$0 to <\$10 million in the economic evaluation, and \$0 to <\$10 million in the financial estimates.

Estimated PBS usage & financial implications

- 6.79 This resubmission was not considered by DUSC.
- 6.80 The resubmission used an epidemiological approach based on the same international estimates of prevalence of SMA in patients aged over 18 years that were used for this patient population in the November 2017 PBAC submission for nusinersen.
- 6.81 Table 14 and Table 15 present the key inputs for financial estimates and estimated use and financial implications of listing adult-initiated nusinersen treatment, respectively.

Table 14: Key inputs for financial estimates

Parameter	Value applied and source	Comment																												
Prevalent population	From the November 2017 PBAC submission's estimates of prevalent patients over 18 years of age with Type I, II or III SMA	Likely underestimated use in adult patients as the prevalent patient pool may be higher, as noted in para 7.4 of the November 2017 PBAC PSD for nusinersen. There was no allowance for use in non-adult patients																												
Uptake rate	20% in Year 1 increasing by 5% per year up to Year 6. Based on clinical opinion.	The evaluation considered this was likely underestimated																												
Price of nusinersen	\$ [redacted] per 5 mg vial with the cost of [redacted] rebated for patients initiating treatment over 18 years of age only	The price was the requested effective price for adult patients, but this price and rebate were not proposed for non-adult patients forming part of the requested restriction																												
Discontinuation rate	Zero discontinuation assumed	Inconsistent with the economic evaluation																												
MBS items	<table border="1"> <thead> <tr> <th>Service</th> <th>Cost</th> <th>80% rebate</th> <th>MBS item</th> </tr> </thead> <tbody> <tr> <td>Specialist consultation</td> <td>\$44.35</td> <td>\$35.48</td> <td>105</td> </tr> <tr> <td>Pre-anaesthesia consultation by anaesthetist</td> <td>\$44.35</td> <td>\$35.48</td> <td>17610</td> </tr> <tr> <td>Initiation of management of anaesthesia for lumbar puncture</td> <td>\$100.50</td> <td>\$80.40</td> <td>21945</td> </tr> <tr> <td>Anaesthesia, perfusion or assistance at anaesthesia, less than 15 minutes</td> <td>\$20.10</td> <td>\$16.08</td> <td>23010</td> </tr> <tr> <td>Intrathecal infusion of a therapeutic substance</td> <td>\$192.95</td> <td>\$154.36</td> <td>18216</td> </tr> <tr> <td>Total cost per administration</td> <td>\$402.25</td> <td>\$321.80</td> <td>Calculated</td> </tr> </tbody> </table>	Service	Cost	80% rebate	MBS item	Specialist consultation	\$44.35	\$35.48	105	Pre-anaesthesia consultation by anaesthetist	\$44.35	\$35.48	17610	Initiation of management of anaesthesia for lumbar puncture	\$100.50	\$80.40	21945	Anaesthesia, perfusion or assistance at anaesthesia, less than 15 minutes	\$20.10	\$16.08	23010	Intrathecal infusion of a therapeutic substance	\$192.95	\$154.36	18216	Total cost per administration	\$402.25	\$321.80	Calculated	<p>Used appropriately, with 80% rebate for the MBS.</p> <p>The financial estimates did not consider the cost to the MBS of monitoring for thrombocytopenia or renal toxicity which may also be required for patients treated with nusinersen.</p>
	Service	Cost	80% rebate	MBS item																										
	Specialist consultation	\$44.35	\$35.48	105																										
	Pre-anaesthesia consultation by anaesthetist	\$44.35	\$35.48	17610																										
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	Anaesthesia, perfusion or assistance at anaesthesia, less than 15 minutes	\$20.10	\$16.08	23010																										
	Intrathecal infusion of a therapeutic substance	\$192.95	\$154.36	18216																										
Total cost per administration	\$402.25	\$321.80	Calculated																											

Source: Table 4.5, p218 of the resubmission and compiled during the evaluation.

Table 15: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients treated	[redacted] ¹	[redacted] ¹	[redacted] ¹	[redacted] ¹	[redacted] ¹	[redacted] ¹
Number of scripts dispensed ^a	[redacted] ¹	[redacted] ¹	[redacted] ¹	[redacted] ¹	[redacted] ¹	[redacted] ¹
Net financial implications						
Net cost to PBS/RPBS ^a	\$ [redacted] ²	\$ [redacted] ²	\$ [redacted] ²	\$ [redacted] ³	\$ [redacted] ³	\$ [redacted] ³
Net cost to MBS	\$ [redacted] ⁴	\$ [redacted] ⁴	\$ [redacted] ⁴	\$ [redacted] ⁴	\$ [redacted] ⁴	\$ [redacted] ⁴
Net cost of lumbar puncture adverse events	\$ [redacted] ⁴	\$ [redacted] ⁴	\$ [redacted] ⁴	\$ [redacted] ⁴	\$ [redacted] ⁴	\$ [redacted] ⁴
Net cost to PBS/RPBS/MBS	\$ [redacted] ²	\$ [redacted] ²	\$ [redacted] ²	\$ [redacted] ³	\$ [redacted] ³	\$ [redacted] ³
Previous submission November 2017 (net cost is based on the subgroup who are aged over 18 years)						
Net cost to PBS/RPBS for patients aged over 18 years	\$ [redacted] ⁵	\$ [redacted] ⁵	\$ [redacted] ⁶	\$ [redacted] ⁶	\$ [redacted] ⁷	\$ [redacted] ⁸

Source: Tables 4.3 - 4.6, pp216-219 of the resubmission, and Table 4.4.1 November 2017 PBAC commentary for nusinersen.

^a Assuming 3 loading doses and then one script every 4 months, with no discontinuation as estimated by the resubmission, and no co-payments.

The redacted values correspond to the following ranges:

¹<\$500

²\$10 million to <\$20 million

³\$20 million to <\$30 million

⁴\$0 to <\$10 million

⁵\$30 million to <\$40 million

⁶\$40 million to <\$50 million

⁷\$50 million to <\$60 million

⁸\$60 million to <\$70 million

- 6.82 The net cost to the PBS/RPBS of listing nusinersen as requested was estimated to be \$20 to <\$30 million in Year 6, and a total of \$100 to <\$200 million in the first 6 years of listing.
- 6.83 The estimates did not include the likely of use of nusinersen in patients aged 18 years or less not covered by the current restriction (noting the resubmission proposed a higher price and [REDACTED] for these patients). The PSCR stated the size of this population was estimated to be very small and unlikely to have a significant financial impact. Further, the PBAC noted that the risk of not specifically including this population in the financial estimates may be somewhat mitigated through the proposed Risk Sharing Arrangement (RSA).
- 6.84 Overall, the evaluation considered the estimates were highly uncertain given the uncertainty surrounding the likely:
- uptake rate. The resubmission assumed uptake rates of 20% in Year 1 increasing by 5% per year up to Year 6 based on clinical opinion;
 - rates of discontinuation, given the resubmission assumed there would be no discontinuation; and
 - the prevalence of the disease in adult patients. The PBAC previously considered the estimated number of patients with Type II and III SMA to be uncertain and likely underestimated noting these were based on overseas data due to a lack of Australian data (Nusinersen PSD, PBAC meeting November 2017, para 7.23).
- 6.85 Given the average life expectancy of Type II patients is into adulthood and Type III patients have a normal lifespan, the ESC considered that the cost of this treatment will escalate beyond Year 6 as patients will remain on treatment long term and the treated prevalent population will grow. In November 2017, the PBAC considered that Type II and III patients would account for the majority of treatment costs (Nusinersen PSD, PBAC meeting November 2017, para 7.26).
- 6.86 The ESC considered that the age distribution of patients likely to access nusinersen under the requested listing and the likely distribution of patients with Type IIIa or IIIb SMA was uncertain. The ESC noted that the average age of patients in Hagenacker 2020 was 36 years (n = 139), compared with 45 years in the SMA Australian member database, 2020 (n = 181). The resubmission estimated 27% with Type II SMA and 73% with Type III compared with 42% and 47%, respectively, in the SMA Australia member database (n = 182).

Financial Management – Risk Sharing Arrangements

6.87 The sponsor stated that it was willing to enter a RSA to manage uncertainty associated with the size of the adult SMA population and the uptake rate. The RSA proposed was a revision of the existing [REDACTED] for adult patients initiating treatment. The [REDACTED] was applied in the economic and financial analysis presented by the resubmission (i.e. the economic model and financial estimates were based on patients requiring [REDACTED], loading doses) and was proposed to be achieved by tracking initiating patients, as occurs for the existing listing.

Other relevant factors

6.88 The resubmission stated there is an inequity of access issue with the current listing since it precludes initiation of nusinersen in patients >18 years in those with SMA symptom onset prior to 3 years of age (Type I, II or IIIa). The PSCR re-iterated this, arguing that the current restriction 'is not equitable because the current age restriction is a barrier to access for SMA patients with the exact same clinical features born even just one day apart. It is not necessarily efficient because there are adult patients who have the capacity to benefit from treatment with nusinersen being denied access simply because of their date of birth.' The ESC noted the equity issue raised by the PSCR. However, the ESC also noted that the strength of data and cost-effectiveness of an intervention can differ by sub-groups, which necessarily have specific thresholds defining membership of those sub-groups.

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

7 PBAC Outcome

7.1 The PBAC did not recommend extending the listing of nusinersen to include the treatment of spinal muscular atrophy (SMA) in patients with symptom onset prior to 19 years of age, and removal of the age limit of 18 years for initiation of treatment. The PBAC recognised the high clinical need for effective treatments for adults with SMA. However, the PBAC considered that the resubmission had not adequately defined the appropriate adult population for nusinersen and proposed convening a consultation with experts in the clinical management of adult SMA to help resolve the specific issues associated with use of nusinersen in adult patients. The PBAC considered the magnitude of the effect was difficult to quantify and the incremental cost effectiveness ratio (ICER) was >\$1,055,000 per QALY and likely underestimated. The PBAC considered there was a need for work to be progressed on a Decision Support Analysis as described below.

7.2 The PBAC considered that, rather than removing criteria around age, alternative criteria could be considered that identify patients most likely to benefit (e.g. based on level or type of disability). Specialist clinical input would be required to help determine such criteria and thus define the appropriate patient population.

- 7.3 The PBAC agreed with the ESC that specialist clinical input will also be required for a number of other aspects of the restriction, including to help determine:
- continuation criteria, given that 3.5% to 13% of patients may still experience a decline in motor function, upper limb strength or in distance walked in the six-minute walk test (6MWT) despite being treated with nusinersen;
 - the appropriate prescriber/treatment setting for adult patients; and
 - issues around combination therapy with other treatments for SMA.
- 7.4 As such, the PBAC considered that further clarity on the clinical place of nusinersen in a broader population of patients with Types I, II or III SMA is required to inform the appropriate initial and continuing restriction criteria, appropriate population, cost-effectiveness and financial implications of broadening the listing of nusinersen.
- 7.5 The PBAC considered that the nominated comparator, standard care, was appropriate. The PBAC also noted that risdiplam was registered by the FDA on 7 August 2020 for use in patients 2 months of age and older.
- 7.6 The PBAC noted that the proposed restriction includes initiation of nusinersen in three new patient populations:
- 1) patients >18 years with SMA symptom onset prior to 3 years of age (Type I, II or IIIa);
 - 2) patients >18 years with SMA symptom onset between 3 and 18 years of age (Type IIIb); and
 - 3) patients ≤18 years with SMA symptom onset between 3 and 18 years of age (Type IIIb).

Clinical evidence in the form of non-comparative single arm studies was only provided for the first two patient populations.

- 7.7 The PBAC considered that the incremental benefit of nusinersen in the requested population was unclear due to the: lack of randomised comparative data and lack of statistical analyses for the indirect naïve comparisons presented; lack of transitivity between studies, particularly for the studies used to support the outcome of HFMSE noting the unknown impact of variables such as ambulant / non ambulant status, age of patient and rate of decline across types of SMA; the potential for a placebo effect; and the inappropriate exclusion of studies.
- 7.8 The PBAC noted the short duration of follow-up in the included studies in the context of long-term treatment and considered that the durability of response with nusinersen in adults with SMA was unknown. While additional information regarding longer-term follow-up from Hagenacker 2020 were stated in the pre-PBAC response (and at the sponsor hearing), the PBAC noted that these data were not provided and could not be analysed.
- 7.9 Further, the PBAC considered that the importance of the outcomes relied on in the submission, in terms of clinically meaningful benefits for adult patients with SMA, was

unclear and that specialist clinical input may be required to better understand the clinical significance of the outcomes in adults.

- 7.10 The PBAC considered that, while the claim of superior comparative effectiveness compared to standard of care was reasonable, the magnitude and durability of benefit was not able to be quantified based on the data presented.
- 7.11 The PBAC considered that the claim of non-inferior comparative safety was not adequately supported by the data, reiterating its previous consideration that there may be long term implications from repeated lumbar puncture administrations.
- 7.12 The resubmission stated that it intended to submit data from a planned analysis of three prospective, multi-centre, non-randomised registries that are designed to collect longitudinal data on SMA patients irrespective of the treatment received. However, this information remained unavailable at the time of the pre-PBAC response. Overall, the PBAC noted that further data may become available in the near future which may help address some of the aforementioned issues.
- 7.13 The PBAC agreed with the evaluation and ESC that the economic model was highly uncertain as outlined in the 'economic analysis' section. The PBAC considered the key issues included:
- The transition probabilities, the estimates of resource use, and the expected duration of benefit of nusinersen were not derived from the clinical data presented in the comparative effectiveness section. The resubmission's estimated values for these favoured nusinersen and therefore the PBAC considered the ICER was likely to have been significantly underestimated. In particular, the resubmission's estimation of the rate of progression in the standard of care arm contained calculation errors and appeared to have been substantially overestimated.
 - The assumption that the benefit of nusinersen would continue indefinitely for patients remaining on treatment and that all patients who progress on treatment would cease treatment were not adequately substantiated.
 - The appropriateness of the utility weights for the requested population was highly uncertain, as they were based on a small survey of clinicians (n=5) valuing vignettes that were unlikely to capture the health-related quality of life of the patient population.
 - The cost-effectiveness of nusinersen in the group of non-adult patients with symptom onset between 3 and 18 years of age is unclear given this patient population were not included in the model, and given that a higher price and [REDACTED] was inferred for these patients.
- 7.14 The PBAC considered that while many model parameters were optimistic, the ICER was exceptionally high at >\$1,055,000 per QALY for the resubmission base case, or >\$1,055,000 per QALY after correcting for an error in the application of utilities. The PBAC considered that an ICER of this magnitude was not reasonable, noting for context that in March 2018 an indicative ICER of \$300,000 to <\$400,000 per QALY gained was estimated for patients with Type II/IIIa SMA (at the time, this ICER was

considered uncertain and the PBAC advised that a price reduction would be appropriate).

- 7.15 The PBAC considered that the financial estimates were uncertain due to the resubmission's assumptions about the uptake and discontinuation rates for nusinersen. Further, the PBAC reiterated its previous consideration that the estimated number of patients with Type II and III SMA was uncertain noting these were based on overseas data due to a lack of Australian data.
- 7.16 The PBAC considered that the average age of patients likely to access nusinersen under the requested listing and the likely distribution of patients with Type IIIa or IIIb SMA were not adequately defined, noting differences in these patient characteristics between data provided in the resubmission and data provided from the SMA Australian member database, 2020.
- 7.17 The PBAC considered there was significant potential for use outside the requested restriction in adult patients with Type IV SMA.
- 7.18 The PBAC considered that any resubmission would need to be a major resubmission.
- 7.19 The PBAC noted that this submission is eligible for an Independent Review.

Decision Support Analysis

- 7.20 The PBAC noted that there are now a number of therapies available for the treatment of SMA internationally, one of which is currently registered and subsidised in Australia for a defined group of patients. Others are either in development, or being considered for registration by the TGA and for public subsidy by the PBAC. These therapies include nusinersen (sponsored by Biogen), onasemnogene abeparvovec (ONA) and branaplam (sponsored by Novartis) and risdiplam (sponsored by Roche).
- 7.21 The PBAC further noted that up to now, PBAC has been presented with subsidy applications for therapies for SMA sequentially with evidence based on sub-populations and stages of treatment. Submissions for nusinersen were considered at the November 2017, March 2018, July 2018, July 2019, November 2019 and July 2020 PBAC meetings, submissions for nusinersen, and for ONA were considered at the November 2020 PBAC meeting, and further PBAC submissions are expected in 2021.
- 7.22 The PBAC noted that whilst this approach reasonably reflects the different timeframes in which these therapies and/or new clinical data have become available, it means that it has not been in a position to conduct an overall assessment of all available therapies across the whole of this comparatively rare disease for which direct treatments have only become available in the past 5-years.
- 7.23 The PBAC noted this submission-by-submission approach is further complicated because nusinersen, ONA and risdiplam/branaplam have different mechanisms of action or routes of administration. However, at present there is very little information on how these three types of therapies could best be, or are being, used in SMA

patients in clinical practice, for example, as monotherapy, or sequential monotherapy (on failure of prior therapy), or concomitantly in all or certain patients.

- 7.24 The PBAC considered an overall and holistic approach to consideration of the entire treatment algorithm and the strength of all available evidence would better support its decision making, particularly given that only short-term clinical data are available but the claims from each sponsor make varying predictions about the benefits of each treatment into the future which cannot be reconciled by an assessment of individual submissions independently from each other.
- 7.25 For the reasons given above, the PBAC considered it was in the interests of patients and families, prescribers and payers for a decision support analysis for SMA treatment that takes into account all the currently available clinical data and informs a broader “whole of disease” economic and financial analyses.
- 7.26 The PBAC requested the Department convene a stakeholder meeting including clinical experts, consumer representatives and relevant sponsors with the intention of progressing work towards a decision support analysis for SMA. The PBAC considered an appropriate starting point would be for the stakeholder meeting to consider the following issues for each of the two broad groups of patients, pre-symptomatic and symptomatic for whom treatment with one, or more, SMA therapies may be considered. The PBAC noted these issues are intended to be a starting point for discussion and further matters may arise.

Pre-symptomatic

- For diagnosis by genotype alone –
 - What SMN2 copy numbers should be eligible to initiate treatment
 - Should antenatal genetic diagnosis be confirmed by post-natal genetic testing
- First, second and subsequent line treatment options
- Criteria to determine when to move to second or subsequent options
- Concomitant therapy
- Therapy continuation rules
- When to stop therapy

Symptomatic

- Who should be treated: some patients can access now, some not.
 - First line treatment options (if not treated while pre-symptomatic)
 - Criteria to determine when to move to second or subsequent options
 - Concomitant therapy
 - Therapy continuation rules
 - When to stop therapy
- 7.27 The PBAC noted that the limited clinical data available may make it more difficult to conduct robust economic and financial analyses that reflect the preferred treatment algorithm(s). However, the PBAC considered this does not, of itself, justify continuing the current piecemeal approach.

- 7.28 The PBAC noted a disease-based registry, rather than therapy-based registries, may be appropriate for informing the cost-effectiveness of all SMA therapies.

Outcome:

Rejected

8 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.

9 Sponsor's Comment

Biogen welcomes the PBAC acknowledgement of the high clinical need for adults living with SMA. Our resubmission for SPINRAZA treatment in adults living with SMA has shown clinically meaningful benefit for these individuals. Biogen will work as swiftly as possible to address the PBAC feedback on the resubmission to enable timely access for this deserving population of adults with SMA.