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

1 Purpose of Application

1.1 The minor resubmission sought a Section 100 Authority Required listing of nusinersen for the treatment of paediatric patients with infantile-onset or childhood-onset Spinal Muscular Atrophy (SMA) with onset of symptoms prior to 3 years of age.

2 Requested listing

2.1 The minor resubmission proposed that the listing be targeted to the treatment of patients (18 years of age or younger at the commencement of treatment) with infantile-onset or childhood-onset SMA who have genetic documentation of 5q SMN homozygous gene deletion, homozygous gene mutation, or compound heterozygote with onset of signs and symptoms consistent with SMA prior to 3 years of age.

2.2 The proposed restriction wording from the November 2017 major submission is presented below. The minor resubmission did not provide any additional restriction wording, but acknowledged that the final restriction wording needed to be developed.

2.3 Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with strikethrough.

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
NUSINERSEN Initial treatment 12mg/5mL injection, 1 x 5 mL vial	1	3	$[redacted](public)* $[redacted](private)	Spinraza Biogen Australia Pty Ltd
Continuing treatment 12mg/5mL injection, 1 x 5 mL vial	1	2	$[redacted](public)* $[redacted](private)	

*Effective DPMQ = $[redacted]

Category / Program	Section 100 – Highly Specialised Drugs Program
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Episodicity:	

Severity:	Infantile-onset and childhood-onset
Condition:	Spinal muscular atrophy
PBS Indication:	~~Treatment of~~ *Infantile-onset and childhood-onset* spinal muscular atrophy
Restriction Level / Method:	☐Restricted benefit ☒Authority Required - In Writing ☐Authority Required - Telephone ☐Authority Required – Emergency ☐Authority Required - Electronic ☐Streamlined
Treatment phase:	Initial treatment
Treatment criteria:	~~The treatment must be prescribed~~ *Must be treated* by a neurologist, or by a physician in consultation with a neurologist with expertise in the treatment of spinal muscular atrophy; AND ~~The treatment is administered intrathecally by, or under the direction of, healthcare professionals experienced in performing lumbar punctures; AND~~ The treatment must be given concomitantly with standard of care for this condition.
Clinical criteria:	Patient must be diagnosed by a neurologist, or by a physician in consultation with a neurologist with expertise in the treatment of SMA; AND *The treatment must be administered intrathecally by, or under the direction of, healthcare professionals experienced in performing lumbar punctures; AND* Patient must have genetic documentation of 5q survival-of-motor neuron (SMN) homozygous gene deletion, homozygous gene mutation, or compound heterozygote.
Population criteria	Patient must have onset of clinical signs and symptoms consistent with ~~SMA~~ *infantile-onset or childhood-onset SMA* prior to 3 years of age. *Patient must be 18 years of age or less at* ~~initiation of~~ *the commencement with* therapy.
Prescriber Instructions	The authority application must be *made* in writing and must include: (1)a completed authority prescription form; and (2)a signed patient acknowledgement; or an acknowledgement signed by a parent or authorised guardian, if applicable; and (3)a copy of the pathology report detailing the molecular testing for 5q SMN homozygous gene deletion, homozygous gene mutation, or compound heterozygote.
Administrative Advice	Special Pricing Arrangements apply. No increase in the maximum number of repeats may be authorised.

Category / Program	Section 100 – Highly Specialised Drugs Program
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Episodicity:	
Severity:	*Infantile-onset and childhood-onset*
Condition:	*Spinal muscular atrophy*
PBS Indication:	*Infantile-onset and childhood-onset spinal muscular atrophy*

Restriction Level / Method:	☐Restricted benefit ☒Authority Required - In Writing ☐Authority Required - Telephone ☐Authority Required – Emergency ☐Authority Required - Electronic ☐Streamlined
Treatment phase:	*Continuing treatment*
Treatment criteria:	*Must be treated by a neurologist, or by a physician in consultation with a neurologist with expertise in the treatment of spinal muscular atrophy; AND* *The treatment must be given concomitantly with standard of care for this condition.*
Clinical criteria:	*Patient must have previously received PBS-subsidised treatment with this drug for this condition.*
Population criteria	*Patient must have onset of clinical signs and symptoms consistent with infantile-onset or childhood-onset SMA prior to 3 years of age.*
Prescriber Instructions	*The authority application must be made in writing and must include:* *(1)a completed authority prescription form; and* *(2)a signed patient acknowledgement; or an acknowledgement signed by a parent or authorised guardian, if applicable.*
Administrative Advice	*Special Pricing Arrangements apply.* *No increase in the maximum number of repeats may be authorised.*

2.4 The proposed eligible patient population is narrower than the proposed eligible patient population in the November 2017 major submission (patients with infantile-onset and childhood-onset SMA) because Type IIIb and c patients are not included and because treatment with nusinersen must commence before a patient turns 19.

2.5 The November 2017 major submission proposed a price of $[redacted] per vial and a special pricing arrangement consisting of a [redacted]% rebate for the cost of [redacted] loading doses. This effectively reduced the DPMQ for initial treatment to $[redacted] per vial for the [redacted] loading doses.

2.6 The resubmission proposed an effective price of $[redacted] per vial achieved through a special pricing arrangement (SPA) consisting of a [redacted]% rebate on the proposed published price of $[redacted] per vial. The resubmission stated that this proposal does not include an additional rebate on the loading doses.

3 Background

3.1 At its November 2017 meeting, the PBAC did not recommend the listing of nusinersen for the treatment of patients with Infantile-onset (Type I) and childhood-onset (Types II & III) SMA on the basis of uncertainty about the clinical effectiveness of nusinersen in terms of the extent and durability of response across the spectrum of SMA for which subsidy was sought. The PBAC considered that the submission contained insufficient information to form a view on the cost-effectiveness of treatment with nusinersen across the spectrum of SMA. However, the PBAC

acknowledged there is a high and urgent clinical need for treatments for SMA, particularly for the most severe forms of the condition and noted that consumer input was strongly supportive of a broad PBS listing across all forms of SMA, including adult onset disease. The PBAC considered that further information on the cost-effectiveness of treatment with nusinersen is necessary in order for it to be able to form a view on the appropriate PBS subsidy price, but that based on the information available, it is likely that a substantial reduction in the proposed price will be required.

3.2 Subsequent to the November 2017 PBAC meeting, the sponsor submitted a minor submission for consideration at the March 2018 PBAC meeting which sought listing for the treatment of infantile-onset (Type I) SMA only.

3.3 A nusinersen stakeholder meeting for the purpose of informing the PBAC of clinical parameters which may be used to identify SMA patients with the severest forms of the condition in high need of treatment was held on January 18 2018. The stakeholder meeting was attended by members of the PBAC, health practitioners with expertise in the treatment of SMA, the CEO of SMA Australia, a patient representative and representatives of the sponsor (Biogen). Input to the PBAC from stakeholders in the discussion during the meeting indicated that the age of symptom onset was the strongest predictor of prognosis and as such, young patients with early symptom onset (before 3 years of age) are those in highest need of new treatment options due to the severity of their condition relative to SMA patients with later symptom onset.

3.4 Based on the outcomes of the nusinersen stakeholder meeting, the sponsor revised its proposal for subsidy of nusinersen for PBAC consideration at the March 2018 meeting to include all SMA patients with symptom onset prior to 3 years of age.

3.5 The outstanding matters of concerns from the previous November 2017 PBAC meeting are summarised in the table below.

Table 1: Summary of outstanding matters of concern

Matter of concern (November 2017 Public Summary Document)	How the resubmission addressed it
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]	Indicative cost/QALY gained presented for Type I and separately for Type II/IIIa.
The PBAC noted that the evidence from ENDEAR showed that treatment with nusinersen in patients with Type I SMA resulted in improvements in the primary outcomes of motor milestone response (MRR) and event free survival (EFS) over the duration of follow up in the trial. However the median time to event had not been reached in the nusinersen treatment arm at the last follow up (December 2016), so the extent of the event free survival benefit is not yet clear [para 7.10].	Provided updated results for the Type I SMA patients who crossed-over into the open label extension SHINE from the ENDEAR trial. The median time to event was reported to be 73.0 weeks (95% CI: 36.3, not estimated).

Matter of concern (November 2017 Public Summary Document)	How the resubmission addressed it
The PBAC noted the mean improvement in Hammersmith Functional Motor Scale – Expanded (HFMSE) score of 3.9 points in the nusinersen treatment group compared to the decline of -1.0 points in the sham-control group in the CHERISH trial. However the PBAC considered further information is needed to establish the clinical relevance of this change. The PBAC considered that the submission's nomination of 3-point change in HFMSE score as a minimally clinically important difference (MCID) was not adequately supported [para 7.11].	No additional data provided to support clinical significance of 3-point change in HFMSE score. Input to the PBAC at the nusinersen stakeholder meeting indicated that the HFMSE score is not particularly sensitive to small changes in patient functioning, particularly at the lower end of the scale. Patients can demonstrate an improvement in function without a change in HFMSE score. Further, stakeholder input also indicated that a stable HFMSE score is clinically meaningful particularly in younger patients with progressive disease.
The PBAC considered that the evidence presented for Type III SMA, a naïve comparison of the data from 25 patients in the single-arm non-randomised open-label study CS12, versus data on the natural history of SMA was not sufficient to establish comparative efficacy in Type III SMA [para 7.14].	No additional clinical data provided for Type III SMA patients.
The PBAC agreed with its ESC that it would have been more appropriate to apply the hazard ratio for EFS in the model (HR=0.530) rather than that for OS (HR=0.372) from the ENDEAR trial in the base-case [para 7.19].	No change in approach to using OS hazard ratio rather than EFS hazard ratio in model.
The PBAC considered that the cost per responder estimates presented for Type II and Type III SMA were highly uncertain [para 7.20].	Indicative cost/QALY gained presented.
The PBAC advised that a resubmission presenting a model based on 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].	Price reduced from $[redacted] per vial with [redacted] loading doses rebated to $[redacted] with [redacted] rebated. Indicative cost utility analysis presented.
The PBAC noted that the incidence of Type I SMA was estimated based on Australian data and considered this to be reasonable. However, the PBAC 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 [para 7.23].	Presented estimated number of prevalent Type I, Type II and Type IIIa patients ≤ 18 years based on survey of paediatric treatment centres in Australia and data from SMA Australia.
The PBAC considered that Type II and Type III SMA patient population would account for the majority of treatment costs. Given the uncertainties around the size of the patient population and use of this treatment in clinical practice, the PBAC considered that a tight subsidisation cap through an RSA would be required if nusinersen was recommended for listing [para 7.26].	Proposed an RSA. No details provided, except to note this can be used to manage the number of Type II/IIIa SMA patients expected in Year 1 of listing.

Matter of concern (November 2017 Public Summary Document)	How the resubmission addressed it
The PBAC considered that nusinersen may meet the criteria for 'rule of rescue' for SMA Type I where the life expectancy of patients without treatment is only two years, however there remains uncertainty about the duration of benefit of treatment in SMA Type I given the duration of follow up on the ENDEAR trial (13 months) . The PBAC did not consider the 'rule of rescue' criteria met for SMA Type II. In particular, criterion four, that 'the proposed medicine provides a worthwhile clinical improvement sufficient to qualify as a rescue from the medical condition' is not met for SMA Type II, noting the uncertain clinical significance of a 3-point HFMSE score and uncertain long-term benefit of treatment given the duration of the CHERISH trial (15 months). The PBAC considered there was insufficient clinical data to ascertain whether the 'rule of rescue' criteria would be met for SMA Type III.	Claimed that the proposed eligible patient population of patients with genetic documentation of 5q SMN homozygous gene deletion, homozygous gene mutation, or compound heterozygote with onset of signs and symptoms consistent with SMA prior to 3 years of age, would be considered to meet the rule of rescue.

4 Population and disease

4.1 SMA is an autosomal recessive neuromuscular disease caused by mutations or deletions in the survival-of-motor-neuron 1 (SMN-1) 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. Respiratory muscle failure is the major cause of morbidity and mortality for patients with SMA. The SMN-2 gene also produces SMN protein albeit at low levels which are not sufficient to sustain survival of spinal motor neuron function. As SMN-2 copy number varies from patient to patient, there is a clinical spectrum of the disease where fewer SMN-2 gene copies correlate to earlier age of onset and increased disease severity. SMA is classified into types (0, I, II, III and IV) based on age of onset and maximal motor function achieved. Details of the types and typical features of each SMA type are shown below.

Table 2: Classification of SMA based on age of onset and maximal motor function achieved

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

Source: Table 1.1.1, p5 of the November 2017 submission
SMA = spinal muscular atrophy; SMN-2 = survival-of-motor-neuron 2 gene
* Need for respiratory support at birth; contractures at birth, reduced foetal movements.
^ Prognosis varies with phenotype and standard of care interventions
\# Ia joint contractures present at birth; Ic may achieve head control.
Note: The most common number of copies of the SMN-2 gene for each type of SMA is bolded.

4.2 Stakeholder input to the PBAC at the nusinersen stakeholder meeting indicated that it can be difficult to distinguish between Type I and Type II SMA as there is a large overlap in clinical presentation in these two patient groups. Stakeholder input also indicated young patients with early symptom onset (before 3 years of age) are those in highest need of new treatment options due to the severity of their condition relative to SMA patients with later symptom onset.

5 Consideration of the evidence

Sponsor hearing

5.1 There was no hearing for this item as it was a minor submission.

Consumer comments

5.2 The PBAC noted and welcomed the input from individuals (191), health professionals (38) and Muscular Dystrophy Queensland via the Consumer Comments facility on the PBS website. The comments described the burden of SMA on both patients and families and emphasised the need for treatments to slow disease progression. The comments also described benefits of treatment including improved motor function, independence and quality of life.

5.3 Muscular Dystrophy Queensland indicated its support for nusinersen to be PBS-listed for the treatment of SMA and emphasised the positive outcomes of treatment from

the sponsor's trial with Type I SMA patients. The correspondence further emphasised the importance for patients to be able to access and begin treatment early in the course of the disease.

Clinical trials

5.4 As a minor submission, no new clinical trials were presented in the minor resubmission.

5.5 The November 2017 major submission was based on two head-to-head trials comparing nusinersen to sham-control:

- ENDEAR (n=121) in infantile-onset SMA (Type I) and
- CHERISH (n=126) in childhood-onset SMA (Type II).

Supplementary single-arm trials CS3A for infantile-onset SMA Type I (n=20) and CS12 for childhood-onset SMA Types II & III (n=47) were also presented in the November 2017 major submission.

5.6 The pre-PBAC response to the March 2018 meeting provided the results from the first interim analysis of the SHINE (CS11) study. A cohort of patients from the ENDEAR and CHERISH trials continued to receive nusinersen, or where crossed over from the control arm to receive nusinersen in this study.

Comparative effectiveness

5.7 The trial results remain unchanged from the previous major submission considered in November 2017.

5.8 Results for the primary outcome of event-free survival (time to death or permanent ventilation) from the ENDEAR trial are presented below.

Table 3: Summary of event-free survival based on Expert Advisory Committee review – ITT analysis, ENDEAR trial

Parameter	Sham-controls	Nusinersen
Number of patients (%)	41 (100)	80 (100)
Number of events (%)	28 (68)	31 (39)
Median time to event	22.6 weeks	Not reached
95% CI for median time to event	13.6, 31.3	36.3, NA
Event rate[a] at: 3 months 6 months 9 months 12 months 13 months	[redacted]	[redacted]
p-value compared to control[b]	0.0046*	
Hazard ratio of nusinersen to controls (95% CI)	0.530 (0.3156, 0.8902)	
p-value compared to control[c]	0.0164	

Source: Table 2.5.6, p112 of the November 2017 submission
C I= confidence interval.
[a] Based on the Kaplan-Meier product-limit method.
[b] Based on log-rank test stratified by disease duration.
[c] Based on Cox proportional hazards model adjusted for each subject's disease duration at screening.

5.9 At the time of the November PBAC consideration, the reported median time to event was 22.6 weeks in the sham-control group (95% CI: 13.6, 31.3), with median time to an event not being reached in the nusinersen treatment arm (95% CI: 36.3, NA). The submission calculated a hazard ratio (using a cox proportional hazards model to adjust for disease duration at screening) of 0.530 (95% CI: 0.316, 0.890; p=0.0164). The pre-PBAC Response to the March PBAC meeting provided updated results for the Type I SMA patients from the open label extension SHINE, into which all patients from the ENDEAR trial crossed-over after 56 weeks (13 months) The pre-PBAC response reported that the median time to event had now been reached in the nusinersen group (73.0 weeks; 95% CI: 36.3, not estimated). The PBAC noted that SHINE was non-comparative and included Type I SMA patients previously in the sham control arm of the ENDEAR trial.

5.10 The primary outcome in the CHERISH trial for patients with Type II SMA was change in Hammersmith Functional Motor scale Expanded (HFMSE) sore. The change from baseline in HFMSE score in the CHERISH trial is presented below.

Table 4: Change from baseline in HFMSE to month 15 (multiple imputation) – ITT set, CHERISH trial

Parameter	Sham-controls	Nusinersen
Number of patients in ITT Set	42 (100)	84 (100)
Number of patients with observed Month 15 value	34 (81)	66 (79)
Number of patients with imputed Month 15 value	8 (19)	18 (21)
Change in HFSME to Month 15 Least squares mean (95% CI)[a] SE	 -1.0 (-2.5, 0.5) 0.76	 3.9 (3.0, 4.9) 0.49
Least squares mean difference (95% CI)[a]	4.9 (3.1, 6.7)	
SE	0.91	
p-value (compared to control)[a]	0.0000001	

Source: Table 2.5.16, p142 of the November 2017 submission
ANCOVA = analysis of covariance; CI = confidence interval; ITT = intention to treat; MI = multiple imputation; SE =, standard error; HFMSE = Hammersmith Functional Motor Scale-Expanded
Note: This table is based on multiply imputed data.
[a] From MI procedure, based on ANCOVA with treatment as a fixed effect and adjustment for each subject's age at screening and HFMSE at baseline. These estimates are constructed from fitting the ANCOVA model to each of the imputed datasets.

5.11 Results from the CHERISH trial indicated that at Month 15, a significantly higher proportion of patients treatment with nusinersen achieved an increase of 3 or more points in HFMSE compared to sham-control (56.8% vs. 26.3%, p=0.00006). The November 2017 submission considered that a 3-point increase in HFMSE would be clinically significant for patients with childhood-onset SMA. The submission explained that the ability to roll and sit up in bed independently would require a 3-point change in specific items of the HFMSE.

5.12 The PBAC noted that the evidence in the submission indicated that the magnitude of benefit from treatment may vary depending on the stage of the disease when treatment is initiated with a larger benefit associated with earlier treatment (paragraph 7.12, November 2017 PBAC Public Summary Document).

5.13 At the nusinersen stakeholder meeting, stakeholder input indicated that the HFMSE is not particularly sensitive to small changes in patient functioning, particularly at the lower end of the scale. Further, it was indicated that a stable HFMSE score is also clinically meaningful particularly in younger patients with progressive disease. Based on this information provided at the stakeholder meeting, the PBAC considered that mean improvement in HFMSE 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.

5.14 The CHERISH study assessed patient and caregiver relevant outcomes using the Paediatric Quality of Life Inventory (PedsQL™) and Assessment of Caregiver Experience with Neuromuscular Disease (ACEND). The results of the PedsQL completed by a subset of patients, showed improvements in all components of the generic PedsQL scale in the nusinersen group while the control group showed

declines in all components except that of social functioning. The effect of providing physical and general care for a child with SMA on the caregiver was evaluated using the ACEND questionnaire. The scores demonstrated a reduction in caregiver burden in the domains of feeding/grooming/dressing, transfer and mobility in the nusinersen group which continued to improve over time. In contrast, caregiver burden was shown to increase over time in the control group for the same domains. The reduction in caregiver burden in the domains of feeding/grooming/dressing, transfer, mobility and sitting/playing in the nusinersen group was either trending towards statistical significance or statistically significant at month 15.

Comparative harms

5.15 The adverse event rates were similar for sham-control compared to nusinersen in the ENDEAR and CHERISH trials.

Clinical claim

5.16 Consistent with the November 2017 major submission, the minor resubmission claimed that nusinersen is superior in terms of comparative effectiveness and no worse in terms of safety compared to sham-control.

5.17 For PBAC's view on this claim, see section 6 PBAC outcome.

Economic analysis

Cost-effectiveness of nusinersen for the treatment of Type I SMA

5.18 The November 2017 major submission presented separate cost-effectiveness analyses for each of the SMA types included in the proposed eligible population (Type I, II & III). The cost-effectiveness analysis for Type I SMA presented in the November 2017 submission presented the results as a cost per life year (LY) gained. Only the costs of nusinersen and its administration were considered. The LYs for standard of care (SoC) were estimated from the event-free survival reported for the ENDEAR trial and extrapolated by fitting a Weibull model using data from a natural history study of SMA (Farrar 2013). The LYs for nusinersen were estimated by applying an HR of 0.372 based on that observed for overall survival in ENDEAR trial. The PBAC noted that from the additional sensitivity analysis presented in the pre-PBAC Response, applying the HR for OS (HR=0.530) did not significantly impact the cost per QALY.

5.19 The following changes were made to the cost-effectiveness analysis for SMA Type I presented in the November 2017 major submission:

- Inclusion of reduced nusinersen price of $[redacted] per vial;
- Inclusion of direct medical, direct non-medical and indirect costs for the

treatment of SMA; and

- Transformation of the LYs gained to quality adjusted life years (QALYs) gained.

5.20 As a minor submission, the revised economic analysis was not evaluated. The sources of data and results are described below.

5.21 As for the November 2017 submission, the duration of nusinersen treatment was based on the extrapolated event-free survival from the ENDEAR trial. It was estimated that patients would require an average of [redacted] injections which is equivalent to [redacted] years of treatment.

5.22 The medical, non-medical and indirect costs were sourced from a German cross-sectional study assessing the cost of illness of SMA (Klug et al 2016). The costs were converted to Australian dollars using an exchange rate of 1.0 EUR to 1.57586 AUD (rate as at 16th February 2017).

5.23 The minor resubmission assumed that costs for patients treated with nusinersen would be the same as for SMA Type III patients, and for SoC the costs would be the same as for SMA Type I patients. The minor resubmission noted this assumption is based on the results of the ENDEAR trial and CS3A study in which patients treated with nusinersen exceeded expectations with respect to motor function and milestones in comparison to those untreated and the natural history of SMA Type I, and that some nusinersen treated patients were able to achieve motor milestones typical of later SMA types, such as Type III SMA. The PBAC considered that the applicability of the costs for Type III SMA to Type I SMA patients treated with nusinersen is limited and uncertain as in the German cost of illness study the median age of Type III patients was 33 years compared with 1 year for Type I patients.

5.24 The annual direct medical costs were estimated to be $[redacted] for a Type I SMA patient and in the economic model this was the assumed annual cost for SoC patients. The annual direct medical costs were estimated to be $[redacted] for a Type III SMA patient and hence were assumed in the model for patients treated with nusinersen. The majority of the difference was due to reduced inpatient medical costs.

5.25 The annual direct non-medical costs for Type III/nusinersen treated patients were $[redacted] compared with $[redacted] for Type I/SoC patients. The majority of the difference was due to reduced informal care by non-working parents.

5.26 The annual indirect costs for Type III/nusinersen treated patients were $[redacted] compared with $[redacted] for Type I/SoC patients. The indirect costs reflect economic loss of productivity of the parents caused by factors such as absenteeism and changes to their working situation.

5.27 The annual costs were multiplied by the discounted survival ([redacted] years for nusinersen treated patients and [redacted] years for SoC) to estimate the average cost per patient.

5.28 The minor resubmission identified three studies which estimate utility values for SMA patients and/or carers. Basetida et al 2016 was a cross-sectional parent-proxy study and provided carer utilities. Lloyd et al 2017 was a case vignette study in which five clinical experts provided a proxy assessment using the EuroQol-5 Dimensions youth version (EQ-5D-Y). Thompson et al 2017 was a PedsQL mapping study. The minor resubmission noted the PedsQL mapping study showed little differentiation between changes in motor function, giving a utility range between the worst and the best disease states of 0.73 to 0.88. The study by Lloyd et al 2017 reported a range between -0.24 and 0.72 depending on disease severity.

5.29 The minor resubmission provided utility values for amyotrophic lateral sclerosis (ALS) and Duchenne muscular dystrophy (DMD) as it was noted that like SMA, these diseases are marked by progressive, debilitating muscle weakness that reduce a person's ability to walk, eat and ultimately, breathe. In ALS, disease states comparable to SMA were associated with utilities in the range of -0.01 to 0.63 and DMD disease states were associated with a range from 0.05 to 0.88. The minor resubmission noted these utility ranges were more comparable to the range of utilities derived from clinical experts (Lloyd et al 2017).

5.30 Utility values reported by Lloyd et al 2017 were used in the cost utility analysis. The mean baseline score for a SMA Type I patient was -0.12. The mean score for Type I patients reclassified as Type III was 0.71. These scores were used as a proxy for patients treated with SoC and nusinersen, respectively. Noting the wide range of possible utility values (see paragraph 5.29 above), the PBAC considered that the values applied were uncertain.

5.31 The results of the cost-effectiveness analysis for Type I SMA as presented in the minor resubmission and the November 2017 major submission are presented in Table 5.

Table 5: Results of the indicative economic evaluation for SMA Type I

	Nusinersen	BSC	Incremental
Minor resubmission			
Costs			
Nusinersen	$[redacted]	$[redacted]	$[redacted]
Administration	$[redacted]	$[redacted]	$[redacted]
Direct medical costs	$[redacted]	$[redacted]	-$[redacted]
Direct non-medical costs	$[redacted]	$[redacted]	$[redacted]
Indirect costs	$[redacted]	$[redacted]	-$[redacted]
Total	$[redacted]	$[redacted]	$[redacted]
Outcomes			
Lys	3.5685	1.0858	2.4827
QALYs	[redacted]	[redacted]	[redacted]
ICERs			
1. Nusinersen and administration costs only (as per November 2017 submission) Cost per LYG Cost per QALY gained			 $[redacted] $[redacted]
2. Scenario 1 with inclusion of direct medical costs (health care perspective) Cost per LYG Cost per QALY gained			 $[redacted] $[redacted]
3. Scenario 2 with inclusion of non-medical and indirect costs (societal perspective) Cost per LYG Cost per QALY gained			 $[redacted] $[redacted]
November 2017 submission			
Costs			
Nusinersen	$[redacted]	$[redacted]	$[redacted]
Administration[a]	$[redacted]	$[redacted]	$[redacted]
Total	$[redacted]	$[redacted]	$[redacted]
Outcomes			
Lys	3.5685	1.0858	2.4827
ICERs			
Cost per LYG			**$**[redacted]

Source: March 2018 minor resubmission, Table 8; November 17 PBAC Minutes Table 12.
[a] reduced due to proposed rebate for 2 loading doses also being applied to the administration costs.
Grey shading indicates data previously seen by the PBAC.

The redacted table shows ICERs of more than $200,000/QALY.

5.32 The reduced cost per vial of nusinersen compared with the November 2017 submission reduced the total discounted cost per patient for nusinersen to $[redacted] from $[redacted]. This is based on patients receiving an average of [redacted] vials (in the November 2017 major submission [redacted] loading doses were proposed to be rebated). The reduced nusinersen price reduced the cost/LYG to

more than $200,000 from more than $200,000.

5.33 The minor resubmission estimated that treatment with nusinersen would result in savings of $[redacted] due to reduced medical resource use. As noted previously this is primarily due to reduced inpatient care. Incorporating the estimated savings in direct medical costs reduced the cost per LYG to more than $200,000 from more than $200,000.

5.34 The minor resubmission estimated that treatment with nusinersen would result in additional costs of $[redacted] due to increased use of non-medical resources. The increased cost for patients treated with nusinersen reflects the increased survival. As noted previously the non-medical costs primarily relate to informal care by non-working parents.

5.35 The minor resubmission estimated that treatment with nusinersen would result in an average saving of $[redacted] per patient due to indirect costs.

5.36 Including the non-medical costs and indirect costs increased the cost/LYG to more than $200,000 from more than $200,000.

5.37 The minor resubmission converted the cost/LYG to a cost/QALY gained based on a utility value of 0.71 for nusinersen treated patients and -0.12 for SoC patients. Overall, it was estimated that treatment with nusinersen would result in an increase of [redacted] QALYs. More QALYs were estimated to be gained compared with LYs (2.48) due to nusinersen treatment increasing quality of life in addition to quantity of life. The cost per QALY gained was estimated to be more than $200,000 based on a health care perspective or more than $200,000 based on a societal perspective with the inclusion of non-medical and indirect costs.

5.38 The minor resubmission estimated if the [redacted] loading doses of nusinersen in the first year of treatment are excluded from the analysis, the cost/LY and cost/QALY gained are more than $200,000 and more than $200,000 (health care perspective), respectively.

Cost-effectiveness of nusinersen for the treatment of Type II/IIIa SMA

5.39 The cost-effectiveness analysis for Type II SMA presented in the November 2017 submission presented the results as a cost per responder. Only the costs of nusinersen and its administration were considered. Responders were defined as those with a ≥3 point increase in HFSME over 15 months.

5.40 The following changes were made to the cost-effectiveness analysis presented in the November 2017 submission:

- Inclusion of reduced nusinersen price;

- Inclusion of direct medical, direct non-medical and indirect costs for the treatment of SMA; and
- Estimation of QALYs gained and results presented as cost per QALY gained.

5.41 The PBAC noted that as a minor submission, the revised economic analysis was not evaluated. The sources of data and results are described below.

5.42 The analysis was based on a time horizon of 12 months.

5.43 Loading doses were not costed and hence the annual cost of nusinersen treatment was based on 3 doses (3 x $[redacted] = $[redacted]). The PBAC noted this was based on the TGA recommended dose, however, in the CHERISH and CS12 trials patients were dosed every 6 months. The PBAC considered that the discrepancy between the dosing regimen in the trials and what would occur in clinical practice (4 monthly dosing) was a remaining factor of uncertainty in assessing the cost-effectiveness of nusinersen for the treatment of SMA.

5.44 As for the Type I analysis the medical, non-medical and indirect costs were sourced from the German cost of illness study (Klug et al 2016).

5.45 The minor resubmission assumed the costs for Type II/IIIa patients treated with nusinersen would be the same as for SMA Type III patients, and for SoC the costs would be the same as for SMA Type II patients. The minor resubmission noted this assumption is based on the results of the CHERISH trial and CS12 study in which patients treated with nusinersen exceeded expectations with respect to motor function and milestones in comparison to those untreated and the natural history of SMA Type II, and that some nusinersen treated patients were able to achieve motor milestones typical of later SMA types, such as Type III SMA. The PBAC considered the applicability of the costs for Type III SMA to Type II SMA patients treated with nusinersen is uncertain as in Klug et al 2016, the median age of Type III patients was 33 years compared with 11 years for Type II patients.

5.46 The annual direct medical costs were estimated to be $[redacted] for a Type II SMA patient and in the economic model this was the assumed annual cost for SoC patients. The annual direct medical costs were estimated to be $[redacted] for a Type III SMA patient and hence were assumed in the model for patients treated with nusinersen. The majority of the difference was due to reduced inpatient medical costs, costs for medical aids and costs for respiratory management.

5.47 The annual direct non-medical costs for Type III/nusinersen treated patients were $[redacted] compared with $[redacted] for Type II/SoC patients. The majority of the difference was due to reduced informal care by non-working parents and costs for housing.

5.48 The annual indirect costs were lower for Type III/nusinersen treated patients were $[redacted] compared with $[redacted] for Type II/SoC patients. The indirect costs reflect economic loss of productivity of the parents caused by absenteeism, invalidity or changes to their working situation.

5.49 As for the Type I analysis the utility values were sourced from Lloyd et al 2017. The mean baseline score for a SMA Type II patient was 0.04. The mean score for Type I patients reclassified as Type III was 0.71. These scores were used as a proxy for Type II/IIIa patients treated with SoC and nusinersen, respectively. The assumed utility value for patients treated with nusinersen (0.71) is similar to the value reported for Type II patients able to stand/walk unaided (0.72).

5.50 The results of the cost-effectiveness analysis for Type II/IIIa SMA as presented in the minor resubmission and the November 2017 submission are presented in Table 6.

Table 6: Results of the indicative economic evaluation for SMA Type II/IIIa

	Nusinersen	BSC	Incremental
Minor resubmission, 12 month time horizon			
Costs			
Nusinersen (3 infusions)	$[redacted]	$[redacted]	$[redacted]
Administration	$[redacted]	$[redacted]	$[redacted]
Direct medical costs	$[redacted]	$[redacted]	-$[redacted]
Direct non-medical costs	$[redacted]	$[redacted]	-$[redacted]
Indirect costs	$[redacted]	$[redacted]	-$[redacted]
Total	$[redacted]	$[redacted]	$[redacted]
Outcomes			
QALYs	[redacted]	[redacted]	[redacted]
ICERs			
1. Nusinersen and administration costs only Cost per QALY gained			$[redacted]
2. Scenario 1 with inclusion of direct medical costs (health care perspective) Cost per QALY gained			$[redacted]
3. Scenario 3 with inclusion of non-medical and indirect costs (societal perspective) Cost per QALY gained			$[redacted]
November 2017 submission, Type II, 15 month time horizon			
Costs			
Nusinersen (4.97 infusions)	$[redacted]	$[redacted]	$[redacted]
Administration	$[redacted]	$[redacted]	$[redacted]
Total	$[redacted]	$[redacted]	$[redacted]
Outcomes			
Responder (≥3 point increase in HFSME over 15 months)	[redacted]%	[redacted]%	[redacted]%
ICERs			
Cost per Responder			**$[redacted]**

Source: Commentary for November 2017 submission, Table 3.8.3; March 2018 resubmission, Table 9
ICER = incremental cost effectiveness ratio; QALY = quality adjusted life year
Grey shading indicates data previously seen by the PBAC.

The redacted table shows ICERs of over $200,000/QALY.

5.51 The cost per QALY gained for Type II/IIIa SMA is estimated to be lower than for Type I SMA despite no survival gain assumed for Type II/IIIa patients treated with nusinersen and the utility gain being smaller (0.67 for Type II/IIIa compared with 0.83 for Type I). The reasons for this include:

- Nusinersen loading doses are not costed in the analysis for Type II/IIIa. When the loading doses are excluded from the analysis for Type I patients the cost/QALY gained is more than $200,000 (health care perspective) which is

lower than that estimated for Type II/IIIa (more than $200,000) (see paragraph 5.35).

- Limiting the analysis for Type II/IIIa to a time horizon of one year. This relies on the assumption of constant costs and benefits over time, and no discounting was applied. Discounting the costs and benefits by [redacted]% per annum in the analysis for Type I patients increases the ICER (for example, from more than $200,000 to more than $200,000 per QALY gained for the scenario including drug and administration costs only).

- The increase in survival for Type I patients leads to increased medical, non-medical and indirect costs.
- Higher non-medical and indirect costs for Type II patients compared with Type I patients and hence larger cost offsets estimated for Type II patients treated with nusinersen.

Drug cost/patient/year

5.52 The drug cost of on-going treatment with nusinersen is $[redacted]/year, based on three maintenance doses per year at the DPMQ of $[redacted]/vial (public).

Estimated PBS usage & financial implications

5.53 The November 2017 major submission took an epidemiological approach, whereby the incident rate of each SMA subtype was applied to the number of live births each year in Australia. Patient survival for each disease subtype was then applied so as to capture the number of prevalent patients for each disease type at the time of nusinersen listing on the PBAC.

5.54 At that time, the PBAC noted that the incidence of Type I SMA was estimated based on Australian data and considered this to be reasonable. However, the PBAC 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.

5.55 The minor resubmission included new Australian data on the prevalence of SMA patients with Type I, II and IIIa SMA who are currently aged ≤18 years and compares this with the patient estimates from the November 2017 submission (Table 7). The new data are derived from a survey of paediatric SMA treatment centres in Australia commissioned by the sponsor, and survey data from the SMA Australia database.

Table 7: Estimated prevalent SMA patients with Type I, III and IIIa who are ≤ 18 years

	Type I	Type II	Type IIIa	Total
PBAC Submission (Table 4.1.5, November 2017 PBAC submission)	[redacted]	[redacted]	[redacted]	[redacted]
PBAC Submission – Treated patient population (Executive Summary, ES8, ES9, November 2017 PBAC submission)	[redacted]	[redacted]	[redacted]	[redacted]
Clinician Survey (National Paediatric Neuromuscular treatment centres (excluding South Australia) – January 2018)	[redacted]	[redacted]	[redacted]	[redacted]
SMA Australia Survey	[redacted]	[redacted]	[redacted]	[redacted]

Source: Table 1 of the Biogen Proposal (dated 19 February 2018).
* PBAC submission estimate is for all Type III SMA patients under 18 years (does not limit to Type IIIa).
** Updated in financial section of the minor resubmission to reflect 25 patients grandfathering (current 21 plus 4 additional prior to PBS listing).

The redacted table shows that the estimated number of prevalent SMA patients, according to all sources, is less than 10,000 in total.

5.56 The minor resubmission noted that while the epidemiological approach used in the submission considered by the PBAC in November 2017 was considered reasonable and based on the best available information at the time, it may potentially overestimate the prevalent patient population compared to the survey data.

5.57 The revised financial estimates presented in the minor resubmission (Table 8) are based on the original approach and data sources, with the number of patients aged over 18 years removed and with an update to the number of Type I patients likely to be grandfathered from the Expanded Access Program. The treatment centre survey data may be preferred for estimating the size of the prevalent SMA population in Australia because it is a relevant, local source for the population in the requested listing. This source indicates that there are [redacted] prevalent patients with Type I, II and IIIa SMA who are <18 years of age compared with [redacted] patients proposed to be treated with nusinersen in the first year of PBS listing. The PBAC considered that data from the paediatric treatment centres is likely to be more precise than the submission's approach whereby an uncertain estimated survival for each disease subtype was applied to Australian (Type I) or overseas (Type II and III) incidence figures to derive the number of prevalent patients. Further the new data provided an estimate of Australian patients with Type IIIa SMA which was not differentiated from all Type III SMA in the submission.

5.58 The SMA Australia data presented in the minor resubmission is based on known cases reported through the organisation. SMA Australia estimated that the database captures 30-50% of the entire SMA community (including Type IV). The proportion of the requested high need population captured in this database is not known.

5.59 The minor resubmission assumed that the uptake rate for incident Type I, II and III SMA patients will be 80%, 100% and 80% respectively. The rates of uptake are unchanged from the previous submission. The DUSC had previously considered that the treatment uptake rates were underestimated. Given the nature of the disease and lack of alternative treatments, DUSC had considered that the uptake rate may approach 100% in all types for incident and prevalent patients (paragraph 6.60, November 2017 PBAC Public Summary Document). The PBAC considered that based on the following information provided at the 18 January 2018 Stakeholder Meeting, uptake may not reach 100% and the Sponsor's original uptake assumptions may be reasonable:

- Some Type I patients would not benefit from nusinersen initiation or not be able to tolerate the procedures
- Some families of Type I SMA patients elect not to commence treatment with nusinersen through the sponsors Expanded Access Program
- The greatest uptake will be expected for the Type II and Type IIIa children as they are the patients at greatest risk of losing function
- The burden of treatment (a four monthly intrathecal injection) may lower uptake in adult patients

5.60 The number of patients, prescriptions and net financial cost to the PBS in the minor resubmission compared with the submission considered in November 2017 are shown in Table 8.

Table 8: Estimated use and financial implications (based on effective price)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use (November 2017)						
Total Type I SMA patients treated per year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total Type II SMA patients treated per year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total Type III SMA patients treated per year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of scripts dispensed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost to the PBS/RPBS (less copayments)	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Estimated extent of use (March 2018)						
Total Type I SMA patients treated per year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total Type II SMA patients treated per year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Type III SMA patients treated per year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of scripts dispensed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost to PBS/RPBS (less copayments)	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]

Source: Section 4 MS Excel Workbooks for the submission to the November 2017 PBAC meeting and the resubmission to the March 2018 PBAC meetings.

The redacted table shows that at year 6, the estimated number of patients was less than 10,000, and the cost to the PBS would be $60 - $100 million.

5.61 The pre-PBAC response presented revised financial estimates which incorporate SMA type II and IIIa Year 1 patient estimates based on the survey of paediatric neuromuscular centres in Australia (see Table 7 above), an assumed uptake rate of 100% for all incident patients, increased uptake for SMA Type II and IIIa and increased continuation rates for SMA Type I patients. The revised patient numbers and financial estimates are presented below in Table 9.

Table 9: Estimated use and financial implications (based on effective price)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use (November 2017)						
Total Type I SMA patients treated per year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total Type II SMA patients treated per year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total Type III SMA patients treated per year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of scripts dispensed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost to the PBS/RPBS (less copayments)	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]

Source: Table 3 of the pre-PBAC Response and updated Section 4 MS Excel Workbooks for the submission to the March 2018 PBAC meeting.

The redacted table shows that at year 6, the estimated number of patients was less than 10,000, and the cost to the PBS would be $30 - $60 million.

5.62 The revised estimated number of prevalent SMA Type I patients were not based on the survey of paediatric neuromuscular centres but instead on the number of SMA Type I patients in the sponsor's Expanded Access Program that would be grandfathered. However, the PBAC noted that the estimated number of prevalent SMA Type I patients ([redacted] based on number of patients to be grandfathered from the sponsor's expanded access program) aligned closely with the corresponding number of patients in the survey ([redacted]).

5.63 The revised estimates also include additional SMA Type II and IIIa patients to account for patients in South Australia that were not captured in the survey. A small number of SMA type II patients were also included to account for any patients not connected to a neuromuscular clinic. The PBAC considered that the inclusion of additional patients to account for patients not treated at a paediatric neuromuscular centre was not justified given the nature of the disease. The PBAC also understood that South Australian patients were receiving treatment through the Paediatric Specialist site in Victoria, and are likely to already be captured in the survey data.

Financial management – risk sharing arrangements

5.64 The resubmission proposed a Risk-Sharing Arrangement (RSA) for nusinersen for the treatment of SMA patients with symptom onset prior to 3 years of age. The resubmission stated that due to the expected large number of Type II and Type III SMA patients initiating treatment in Year 1 of listing, the financial cost in Year 1 would be higher compared with subsequent years and proposed that this be managed through an RSA. The resubmission did not provide any details on the structure of the proposed RSA.

6 PBAC Outcome

6.1 The PBAC recommended the Section 100 (Highly Specialised Drugs Program) listing of nusinersen for the treatment of paediatric patients with infantile-onset or childhood onset Spinal Muscular Atrophy (SMA) with onset of symptoms prior to 3 years of age. The PBAC was satisfied that based on the clinical evidence available, nusinersen provides a significant improvement in efficacy over standard of care for the proposed patient population. However, the PBAC considered there was remaining uncertainty around the extent and durability of treatment effect particularly in Type II/IIIa patients. The PBAC advised that further negotiations with the sponsor were required to address these uncertainties through a combination of mechanisms including a reduction in price, increased rebates or lower financial caps.

6.2 The PBAC again acknowledged the high and urgent clinical need for treatments for SMA, particularly for the most severe forms of the condition and welcomed the many consumer comments received from SMA patients and their families. The PBAC noted the input from the nusinersen stakeholder meeting indicated that young patients (with Type I/II/IIIa SMA) with symptom onset prior to 3 years of age were in the highest need of new treatment options due to the severity of their disease relative to SMA patients with later symptom onset. The PBAC further noted the stakeholder input that it is difficult to distinguish between Type I and Type II SMA due to the large overlap in clinical presentations between these patients. The PBAC therefore considered that the requested listing, which identifies patients based on age of symptom onset would appropriately identify patients with the highest clinical need.

6.3 The PBAC recalled that the primary evidence presented in the November 2017 major submission was based on two head-to-head randomised trials comparing nusinersen and sham-control: ENDEAR in Type I SMA and CHERISH in Type II SMA. The PBAC noted that both trials are of short duration (13 months in ENDEAR and 15 months in CHERISH) in the context of a life-long condition.

6.4 The PBAC noted that the pre-PBAC Response to the March PBAC meeting provided updated results for the Type I SMA patients from the open label extension SHINE, into which all patients from the ENDEAR trial crossed-over after 56 weeks (13 months) The pre-PBAC response reported that the median time to event had now been reached in the nusinersen group (73.0 weeks; 95% CI: 36.3, not estimated). The PBAC noted that SHINE was non-comparative and included Type I SMA patients previously in the sham control arm of the ENDEAR trial. However, these data appear to confirm that treatment with nusinersen in patients with Type I SMA increases life expectancy.

6.5 The PBAC recalled that in the context of older onset SMA, it was previously uncertain

of the clinical significance of a 3-point change in Hammersmith Functional Motor Scale Expanded (HFMSE) score and consequently considered it difficult to interpret the outcomes of the CHERISH trial. The PBAC noted the input from the stakeholder meeting and agreed that the change in HFMSE observed in CHERISH is likely to be clinically meaningful. Furthermore a stable HFMSE score is also meaningful to patients. However overall, the PBAC considered that the long-term efficacy of nusinersen remained uncertain given the limited data available beyond the trial periods, albeit the updated SHINE (CS11) data provided in the pre-PBAC response provides some reassurance that the benefit in terms of HFSME score is maintained for up to 2 years.

6.6 The PBAC noted that there was no comparative data available for SMA Type IIIa patients with the only evidence available being from 25 Type III patients in the single arm, open-label study CS12. The PBAC considered it may be appropriate to extrapolate the evidence of benefit in Type II patients to Type IIIa patients, particularly given that SMA is a spectrum disorder and there is likely to be considerable overlap in the clinical presentation of the disease in patients with different sub-types. However, there remains uncertainty as to whether the extent of benefit across the spectrum of Type IIIa patients will be the same as for Type II patients.

6.7 The PBAC also considered that based on the totality of the data available and in the absence of evidence of a survival benefit for SMA Type II patients or comparative data for SMA Type IIIa patients, it would be reasonable to conclude that the extent of benefit in Type II/IIIa patients is likely to be less than in Type I patients. The PBAC considered a comparison of the durability of response across the different subtypes to be more difficult.

6.8 The PBAC noted that the minor resubmission presented revised economic evaluations: one for SMA Type I and a second for SMA Types II and IIIa combined. The PBAC noted that in contrast to the economic evaluations presented in the November 2017 submission, which modelled cost per life year gained for Type I SMA and cost per responder for Type II and Type III SMA, the revised evaluations incorporate estimates of quality adjusted life years (QALYs), direct medical and non-direct medical costs and the reduced price of $[redacted] per vial.

6.9 The PBAC noted that the cost per QALY gained for Type I SMA (excluding the cost of loading doses consistent with the analysis for Type II/IIIa SMA) was estimated to be more than $200,000 based on a health care perspective and more than $200,000 based on a societal perspective (incorporating non-direct medical costs). The PBAC noted that as per the November 2017 submission, the minor resubmission applied the hazard ratio (HR) for EFS in the model (HR=0.530) rather than that for OS (HR=0.372) from the ENDEAR trial, which it considered would be more appropriate. The pre-PBAC Response presented results of an additional analysis using the EFS

hazard ratio and noted that the incremental cost per QALY did not change significantly as the lower costs associated with worsened survival change in proportion with decreased benefits and therefore have minimal impact on the ICER. The PBAC considered that while the HR for EFS would have been more appropriate to incorporate into the model, the choice of HR had minimal impact on the estimated cost-effectiveness of nusinersen.

6.10 The PBAC noted that the cost per QALY gained for Type II/IIIa SMA was estimated to be more than $200,000 based on a health care perspective and more than $200,000 based on a societal perspective. The PBAC recalled that at its November 2017 meeting, it advised that a cost utility model for Types II and III SMA would be required to establish the cost-effectiveness of treatment compared with standard care. While the PBAC considered that the revised analyses provided with the resubmission were more informative of the likely cost-effectiveness of nusinersen for the treatment of SMA compared with those presented in the November 2017 major submission, it considered that the ICERs presented were still considerably uncertain because:

- All patients treated with nusinersen were assumed to experience the same quality of life as a Type III SMA patient and assigned utility values based on a case vignette study (Lloyd, 2017) reporting proxy assessments from 5 clinicians using the EQ-5D-Y instrument. The baseline utility score applied for patients treated with standard of care was -0.12 and 0.04 for Type I SMA and Type II/IIIa SMA respectively. For Type I SMA and Type II/IIIa patients treated with nusinersen the utility values applied were 0.71 and 0.72 respectively. The PBAC considered the utility values applied to be uncertain, noting that a PedsQL mapping study (Thompson 2017) showed little differentiation between changes in motor function, giving a utility range between the worst and best disease states of 0.73 to 0.88 whereas Lloyd et al 2017 reported a range of utilities between -0.24 and 0.72. The PBAC considered there was a wide range of possible utilities given the range of values reported across the studies.

- The applicability of the direct medical, direct non-medical and indirect costs applied for the treatment of SMA in the analyses to SMA Type I, II and IIIa patients in the Australian clinical setting was uncertain. The minor resubmission assumed that the costs for Type I and II/IIIa patients treated with nusinersen would be the same as or SMA Type III patients. These costs were sourced from a German cost of illness study (Klug et al 2016) where the median age of Type III patients was 33 years. The PBAC noted that for SMA Type I and Type II patients, the median age was 1 year and 11 years respectively in Klug et al 2016.

- The analysis for SMA Type II/IIIa was based on a time horizon of 12 months

and therefore, the assumption of constant costs and benefits over time while the long-term benefit of treatment with nusinersen in the context of a life-time is uncertain.

- The analysis for SMA Type II/IIIa assumes four monthly treatment whereas the comparative clinical evidence for Type II utilised a six monthly treatment regimen, and
- There is no comparative data for nusinersen in Type IIIa SMA.

6.11 The PBAC considered that though the proposed price reduction to $[redacted] per dose from the $[redacted] per dose proposed in the November 2017 major submission was considerable, it did not completely address all the committee's concerns around the uncertainty of the extent and durability of treatment effect particularly in Type II/IIIa patients. As such, the PBAC 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, is necessary to achieve a cost-effective listing. The PBAC considered this could be achieved through (but not limited to), a price reduction, an increased rebate on total annual expenditure, a rebate on the vials used per annum beyond the trial dosing regimen, or a rebate to take into account the proportion of use in SMA IIIa patients for which there are limited efficacy data available.

6.12 The PBAC considered that the survey of paediatric neuromuscular centres in Australia was an appropriate source of data to base the estimated number of prevalent SMA Type II and IIIa patients given there are a limited number of these specialist centres in Australia. The PBAC also noted that while the submission did not estimate the prevalent number of SMA Type I patients based on the survey data, the estimated number of prevalent SMA Type I patients ([redacted] based on number of patients to be grandfathered from the sponsor's expanded access program) aligned closely with the corresponding number of patients in the survey ([redacted]). The PBAC considered that the inclusion of additional patients to account for patients not treated at a paediatric neuromuscular centre was not justified given the nature of the disease.

6.13 The PBAC recalled that the DUSC previously considered the treatment uptake rates (80%, 100% and 80% incident uptake rate for Type I, II and III patients respectively) presented in the November 2017 major submission were underestimated given the nature of the disease and lack of alternative treatments. The PBAC considered that based on the information provided at the nusinersen stakeholder meeting (see above), it may be more reasonable to assume that uptake may not reach 100%. Noting that the median time to event had now been reached in the nusinersen group (73.0 weeks; 95% CI: 36.3, not estimated) in the SHINE study, for patients

previously in the ENDEAR trial, the PBAC considered the increased continuation rates for Type I SMA patients applied in the revised financial estimates was uncertain.

6.14 The PBAC noted that the financial impact of listing nusinersen of $30 - $60 million in Year 1 increasing to $30 - $60 million in Year 6 of listing to be significant albeit considerably less than the estimated financial impact of listing presented in the November 2017 major submission ($60 - $100 million in Year 1 increasing to more than $100 million in Year 6). The PBAC noted that these estimates would need to be revised following further negotiations with the sponsor in line with the PBAC recommendations.

6.15 The PBAC advised that further consultation with clinicians experienced in treating patients with SMA would be required to finalise the restriction. Based on information presented at the nusinersen stakeholder meeting, the PBAC considered that it would be appropriate to include criteria to cease treatment in patients requiring permanent ventilation.

6.16 The PBAC considered it would be appropriate to limit the maximum quantity to one pack with no repeats for continuing treatment.

6.17 The PBAC advised that nusinersen is not suitable for prescribing by nurse practitioners, as drugs listed under Section 100 (Highly Specialised Drugs Program) are currently out of scope for prescribing by Nurse Practitioners.

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

6.19 Under section 101(3BA) of the *National Health Act 1953*, the PBAC advised that nusinersen should not be treated as interchangeable on an individual patient basis with any other medicine.

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

Outcome:
Recommended

7 Recommended listing

7.1 Add new item:

Restriction wording to be finalised.

8 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

9 Sponsor's Comment

Biogen welcomes the positive recommendation for nusinersen for the treatment of paediatric patients with infantile-onset or childhood-onset Spinal Muscular Atrophy (SMA) with onset of symptoms prior to three years of age. However, Biogen is committed to exploring every opportunity to make nusinersen accessible to all those patients in the Spinal Muscular Atrophy community who could benefit from it.