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

1 Purpose of Application

1.1 The standard re-entry resubmission requested a Section 100 (Highly Specialised Drugs Program), Authority Required PBS listing for nusinersen for the treatment of adult patients (older than 18 years of age) diagnosed with spinal muscular atrophy (SMA) with symptom onset before 19 years of age (primarily SMA Types II and III). This listing was requested in addition to the existing paediatric restrictions for nusinersen. This resubmission did not request the funding of nusinersen for adults with symptom onset of SMA at 19 years of age or older (SMA Type IV).

1.2 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 (must be 19 years of age or older) diagnosed with 5q SMA with symptom onset prior to 19 years of age (≤18 years of age). Table 1 provides a summary of the key components of the resubmission.

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

Component	Description
Population	Treatment of adult patients (≥19 years of age) genetically diagnosed with 5q SMA, with symptoms prior to 19 years of age (≤18 years of age).
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	Natural history of SMA with standard of care.
Outcomes	Key efficacy endpoints – motor function: • HFMSE • RULM • 6MWT Key efficacy endpoints – respiratory function: • FVC • Peak cough flow • Safety
Clinical claim	Nusinersen has superior efficacy and non-inferior safety compared to standard of care.

FVC = forced vital capacity; HFMSE = Hammersmith Functional Motor Scale-Expanded; 6MWT = 6 minute walk test; RULM = revised upper limb module; SMA = spinal muscular atrophy
Source: Table 1.2, page xxv and Table 2.30, p139 of the resubmission

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 Nusinersen has been considered by the PBAC on several occasions. The first submission was considered at the November 2017 PBAC meeting. Listing was requested in a broad SMA population comprising patients with infantile-onset (Type I) and childhood-onset (Types II & Type III) with no restrictions proposed regarding the age of nusinersen commencement. This was not recommended by the PBAC.

2.3 A minor resubmission was considered at the March 2018 PBAC meeting for symptomatic SMA patients. At this meeting, nusinersen received a positive recommendation 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 In November 2020, the first resubmission was made to request extending the nusinersen listing to include adults with SMA, specifically in patients with symptom onset prior to 19 years of age and removal of the upper age limit of 18 years for initiation of treatment. This was not recommended by the PBAC.

2.5 A resubmission was considered at the July 2021 PBAC meeting requesting extending the listing of nusinersen to include adults with SMA (>18 years of age) who have experienced signs and symptoms of SMA prior to 19 years of age (≤18 years of age). This was not recommended by the PBAC. The PBAC, however, considered it would be appropriate to extend the current listing for nusinersen in symptomatic patients to include all paediatric patients with Type III SMA, including Type IIIb SMA (i.e. all patients with symptom onset between 3 and 18 years of age, which includes the subset with Type IIIc), to allow equity of access to nusinersen across all paediatric patients with SMA. The PBAC considered that extending the listing to include all paediatric patients would be adequately cost-effective if these additional patients were included in the existing Risk Sharing Arrangement (RSA) for nusinersen without any increase to the existing caps and at the price proposed in the [July 2021] submission (paragraph 7.17, p.49 nusinersen Public Summary Document [PSD], July 2021). At the time of the March 2022 PBAC meeting the extension to the restriction for the Type IIIb paediatric population had not yet been implemented however the pre-PBAC response indicated that the sponsor is willing to progress the PBS listing for Type IIIb patients following a positive recommendation for the adult population.

2.6 The current resubmission requests extending the current PBS listing of nusinersen to include adults with SMA (>18 years of age) who have experienced signs and symptoms of SMA prior to 19 years of age (≤18 years of age). For this patient population, the key matters of concern from the July 2021 PBAC meeting are summarised in Table 2.

Table 2: Summary of outstanding matters of concern

Matter of concern (July 2021 PBAC Meeting)	How the March 2022 resubmission addressed it
PBS restriction	
The PBAC considered that the adult population most likely to benefit from treatment with nusinersen remained inadequately defined in the resubmission (paragraph 7.1).	The sponsor received specialist clinical advice from an adult SMA Advisory Board in September 2021 indicating that: • All eligible adults with SMA should commence treatment with nusinersen, regardless of ambulatory status. • Only adults who are not experiencing a clinically significant loss of motor function should continue treatment with nusinersen. • A loss of motor function is to be assessed by RULM, 6MWT or HFMSE and fine motor function to be assessed using a patient reported outcome measure (SMA-HI or SMAFRS) and should require two consecutive declines on gross and fine motor function. • Assessments should be at 4-6-monthly intervals (coinciding with treatment assessment schedule). • The minimum treatment period should be 18 months, allowing adult patients to have received, at a minimum, 4 loading doses and 3 maintenance doses of nusinersen (consistent with evidence based treatment duration, approximately 15 months). Partially addressed. While input from the Advisory Board was used to determine the PBS restriction including discontinuation criteria, the clinical data and the economic model presented was based only on motor function (RULM, 6MWT and HFMSE) and not SMA-HI or SMAFRS which was not aligned with the proposed restriction.
Clinical Effectiveness	
The PBAC considered that nusinersen provides a minor added benefit, versus standard of care for adult patients with Type II and III SMA, which is clinically relevant (paragraph 7.5). However, the PBAC considered the magnitude and durability of the treatment benefit remained uncertain (paragraph 7.1). The PBAC had also previously expressed that there was a lack of transitivity between studies (Table 2).	This resubmission presented clinical evidence from the regulatory submission for nusinersen in adults to the EMA based on a pooled analysis of 9 real-world studies. The pooled analysis provided an estimate of the magnitude of benefit of nusinersen in adults over 14 months of treatment, to compare the benefit of treatment with nusinersen versus standard of care for the adult SMA population. Not addressed. Of the nine studies presented in the EMA report, eight were included in the July 2021 resubmission. No randomised comparative data or long term data were presented in the resubmission. Concerns regarding the transitivity between studies remain applicable.
The claim of non-inferior comparative safety was not adequately supported by the data, re-iterating the PBAC's previous consideration that there may be long term implications from repeated lumbar puncture administrations (paragraph 7.7).	No safety data was provided in the body of the resubmission. Safety data presented in the EMA application for nusinersen in adults included data from the global safety database (as of 1 March 2021), data from disease registries, post-marketing surveillance studies and published literature. Not addressed. The resubmission again made a claim of non-inferior comparative safety but did not provide evidence to support this claim. No comparison of nusinersen to standard of care with respect to safety was provided.

Matter of concern (July 2021 PBAC Meeting)	How the March 2022 resubmission addressed it
Cost-effectiveness	
The PBAC noted that while the base case ICER of $[redacted][3]/QALY was substantially lower than that in the previous submission ($[redacted][3] million/QALY), it was still considerably higher than the March 2018 indicative ICER of $[redacted][1] estimated for patients with Type II/IIIa SMA (paragraph 7.9).	Partially addressed The economic evaluation was updated to include a revised price offer ($[redacted] per vial reflecting a [redacted]% reduction in current AEMP in the paediatric setting, a [redacted]% reduction from the proposed price in the July 2021 resubmission) The pre-PBAC response proposed a further reduction in the price for nusinersen ($[redacted] per vial) which resulted in an ICER of $[redacted][2]/QALY.
The PBAC considered that the level of confidence in the modelled benefits and the ICER was low and duration of benefit uncertain, and the ICER was likely underestimated (paragraph 7.8, nusinersen PSD, July 2021 PBAC meeting).	Not addressed. The same economic model was used as in the July 2021 resubmission, with the only changes being to the price of nusinersen and administration costs. Consequently, the same observations and limitations noted for the model of the previous resubmission remain relevant.
Financial estimates	
PBAC considered financial estimates were uncertain due to (i) estimated number of patients with Type II and III SMA, (iii) average age of patients likely to access nusinersen and likely distribution of patients with Type IIIa or IIIb patients, (iii) there may be an increase in number of patients treated due to treatment of patients who are currently not seeking any clinical care for their condition (paragraphs 7.13, 7.14, 7.15).	This resubmission presented updated financial estimates, based on the revised price offer ($[redacted] per vial), and estimates the number of adults treated and cost to the PBS (including revised uptake and discontinuation rates). However financial estimates may continue to be underestimated as patient numbers were unchanged from the previous resubmission and uptake rate ([redacted] to [redacted]%) likely remains underestimated given the lack of alternative disease modifying treatments.
Management of uncertainty	
The PBAC advised that a substantial price reduction in combination with a Managed Access Program (MAP) would be required to address the uncertainty around the magnitude and duration of clinical benefit associated with nusinersen treatment and achieve a cost-effective listing in adult patients. The PBAC considered that the price reduction should reflect the benefit of treatment in adult patients relative to that for paediatric patients (paragraph 7.10).	The resubmission reported that following post PBAC meetings held in August and September 2021, it was agreed that that an alternative approach including a more defined continuation criteria, a revised price offer and revised expenditure estimates, including an RSA, could address the areas of uncertainty identified at the July 2021 PBAC meeting. It was also agreed that any clinicians and SMA community would be involved in developing refined continuation criteria. A separate RSA for adults was proposed. The proposed restriction has been changed to address initiation and discontinuation criteria. The PBAC considered that this was adequately addressed as the pre-PBAC response proposed a price that better reflected the benefit of treatment in adult patients relative to that for paediatric patients.

6MWT = 6 minute walk test; AEMP = approved ex-manufacturer price; EMA = European Medicines Agency; HFMSE = Hammersmith Functional Motor Scale-Expanded; PSD = public summary document; RSA = risk share arrangement; RULM = revised upper limb module; SMA = spinal muscular atrophy; SMA-HI = spinal muscular atrophy health index; SMAFRS = spinal muscular atrophy function rating scale
Source: Table 0.1, page xv

The redacted values correspond to the following ranges:
[1]$355,000 to < $455,000
[2]$855,000 to < $955,000
[3]> $1,055,000

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

3 Requested listing

Name, restriction, manner of administration and form	Maximum Quantity (packs)	№.of repeats	Dispensed price for maximum quantity for adult SMA*	Proprietary name and manufacturer
NUSINERSEN				
Initial loading dose			$110,000 published price	Spinraza,
12 mg/ 5 mL injection, 5ml vial	1	3	$[redacted] effective price	Biogen Australia Pty
Maintenance treatment			$110,000 published price	Ltd
12 mg/ 5 mL injection, 5ml vial	1	0	$[redacted] effective price	

Category/Program:	Section 100 – Highly Specialised Drugs Program (Public/Private hospitals)
Prescriber type:	☒ Medical Practitioners
Treatment phase:	Initial treatment of symptomatic SMA - Loading doses
Restriction:	☒ Authority Required (written-only via post or electronic upload through Health Professionals Online Services - HPOS)
PBS indication:	Spinal muscular atrophy (SMA)
Treatment criteria:	Must be treated by a specialist medical practitioner experienced in the diagnosis and management of SMA; or in consultation with a specialist medical practitioner experienced in the diagnosis and management of SMA; AND The condition must have genetic confirmation of 5q homozygous deletion of the survival motor neuron 1 (SMN1) gene; OR The condition must have genetic confirmation of deletion of one copy of the SMN1 gene in addition to a pathogenic/likely pathogenic variant in the remaining single copy of the SMN1 gene; AND The patient must have experienced at least 2 signs or symptoms of SMA prior to 19 years of age; AND The patient must not be receiving invasive permanent assisted ventilation; AND The treatment must not be in combination with other disease-modifying treatments, including risdiplam, for this condition; AND The treatment must be given concomitantly with best supportive 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 19 years of age or older.
Prescribing instructions:	Defined signs and symptoms of SMA are: i) Onset before 19 years of age; and ii) Failure to meet or regression in ability to perform age-appropriate motor milestones; or iii) Proximal weakness; or iv) Hypotonia; or v) Absence of deep tendon reflexes; or vi) Failure to gain weight appropriate for age; or vii) Any active chronic neurogenic changes; or viii) A compound muscle action potential below normative values for an age-matched child. Invasive permanent assisted ventilation means ventilation via tracheostomy tube for greater than or equal to 16 hours per day.
Administrative advice:	No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply.
Treatment phase:	Continuing/maintenance treatment of symptomatic SMA
Restriction:	☒ Authority Required – immediate/real-time assessment (telephone/online PBS Authorities system)
Treatment criteria:	Must be treated by a specialist medical practitioner experienced in the diagnosis and management of SMA; or in consultation with a specialist medical practitioner experienced in the diagnosis and management of SMA; AND Patient must have previously received PBS-subsidised treatment with this drug for this condition; AND

	The treatment must not be in combination with other disease-modifying treatments, including risdiplam, for this condition; AND The treatment must be given concomitantly with best supportive care for this condition; AND The treatment must be ceased when: • There is evidence of a clinically significant decline in motor function due to disease progression, as assessed on two consecutive occasions (4-6 months apart) (compared to baseline), indicating that a patient is no longer receiving benefit with this drug; • A clinically significant decline is defined as: o A decrease in a motor function outcome (RULM, HFMSE, or 6MWT); and o A decrease in a patient reported outcome (SMA-HI or SMAFRS)
Prescribing instructions:	In a patient who wishes to switch from PBS-subsidised risdiplam to PBS-subsidised nusinersen for this condition a wash out period may be required.
Administrative advice:	No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply.

*Effective price applicable only to SMA patients who initiate nusinersen as adults; effective price for treatment initiation as paediatric patients with SMA continues at $[redacted] per dose.
Source: Table 1.5, page xli of the resubmission.

3.1 The revised pricing for adult SMA patients proposed in the resubmission included:

- In addition to the current special pricing arrangement (SPA), a further [redacted]% reduction compared to the current effective price was proposed for the adult population (resulting in an effective price for the adult population of $[redacted]/vial);
- [redacted]; and
- Adult-specific expenditure caps for nusinersen.

3.2 The revised pricing offered in the resubmission was similar to the pricing proposed in the previous resubmission in July 2021 (where [redacted] and an adult specific expenditure cap were also proposed), but a [redacted]% reduction in price for the adult SMA population resulting in an effective price of $[redacted]/vial was offered. The currently proposed effective price of $[redacted]/vial represents a [redacted]% reduction from the proposed price in the July 2021 resubmission.

3.3 In the pre-PBAC response the sponsor proposed a further [redacted]% reduction in price for nusinersen, resulting in an effective price of $[redacted] per vial, with [redacted] loading dose for all adults commencing treatment. This equates to a [redacted]% reduction compared with the existing price per vial of $[redacted].

3.4 In [redacted], the sponsor commenced a program for adults with SMA to allow access to nusinersen treatment prior to PBS listing. The resubmission claimed that patient eligibility criteria for the access program are aligned with the proposed PBS initial treatment, clinical and population criteria proposed in the current resubmission. As of 11 October 2021, there were < 500 adult patients with SMA participating in the program. These patients are accounted for in the Year 1 financial estimates based on the expected number of loading doses these patients would have already received when nusinersen is expected to be listed on the PBS. The Pre-Sub-Committee Response 'PSCR' noted that the sponsor accepts the grandfather listing as proposed

by the Secretariat. The PBAC considered that a grandfather listing for adult SMA patients would be appropriate.

3.5 The submission's proposed discontinuation criteria require that patients demonstrate both a decrease in motor function outcome (which may be more objective) AND a decrease in patient reported outcome in a fine motor function criteria to meet the definition of a clinically significant decline in motor function. The measurement of fine motor function criteria using either the spinal muscular atrophy health index (SMA-HI) or spinal muscular atrophy function rating scale (SMAFRS) was entirely subjective as it is both patient reported and has no clearly defined criteria, with significance based solely on the clinician's discretion. The evaluation considered that a discontinuation criteria which was reliant on the subjective SMA-HI and SMAFRS may lead to continuing use of nusinersen in patients for whom the efficacy and cost effectiveness of nusinersen was unknown, as the clinical evidence and economic evaluation presented by the resubmission was based on the Hammersmith Functional Motor Scale-Expanded (HFMSE), revised upper limb module (RULM) and six minute walk test (6MWT) measurements, with no evidence for SMA-HI and SMAFRS being presented or considered in the economic evaluation.

3.6 The ESC considered that the addition of a continuation assessment to the restrictions, based on patient and clinical expert input, helped to address the PBAC's previous concern that the adult population most likely to benefit from treatment should be adequately defined (paragraph 7.1, nusinersen PSD, July 2021 PBAC Meeting). The PBAC noted that the input from consultation with adults living with SMA indicated that PROs are likely to be useful tools in guiding consultation with the neuromuscular specialist but would not be suitable for inclusion in the restriction as a basis for continuation/discontinuation of treatment. A summary of the consultation process with patients was provided with the consumer comments and is summarised in paragraph 6.7-6.8. The recommendation from consultation with adults living with SMA was that treatment effectiveness should be determined using information from a combination of validated physical assessments, patient reported outcome measures and consultation between the adult living with SMA and the neuromuscular specialist. The PBAC considered that it would be appropriate to amend the proposed restrictions for the continuing listing to reflect this recommendation.

3.7 The evaluation noted that it was uncertain whether the request for adult patients to receive nusinersen for at least 15 months prior to assessment for treatment cessation was appropriate, particularly in patients who continue to experience a decline in motor function in the first 15 months of treatment, and as no included studies treated patients with nusinersen for longer than 14 months. The PBAC noted that in the sponsor hearing the clinician stated that assessment at 6-12 month intervals is feasible within the existing health system and that a 2 year timeframe would be appropriate based on the loading schedule and the current available effectiveness evidence. The PBAC considered the restrictions should require that assessment of suitability for continuation of treatment (evidence of motor function decline) takes place after 2

years of treatment. Under the proposed listing a clinically significant decline in function needs to be assessed over two consecutive occasions 4-6 months apart. The PBAC considered that the requirement for decline in function to be assessed over two consecutive occasions need not be included in the restriction where treatment effectiveness is determined in consultation between the adult living with SMA and the neuromuscular specialist. The PBAC considered that discussions between patients and clinicians regarding benefit from treatment would take into account baseline functioning and prior assessments of gains or decline in function. The PBAC noted that clinicians and patients may choose to discontinue treatment earlier if it is considered to be in the best interest of the patient and considered that these discussions would be expected to occur at each visit with the neurologist after initiation of treatment.

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

4 Population and disease

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

4.2 There is a clinical spectrum of disease with an earlier age of onset being associated with lower numbers of survival motor neuron 2 (SMN2) gene copies and increased severity of symptoms. Table 3 provides an overview of the classification of SMA.

Table 3: Classification of SMA

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	None – 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

*Recent publications distinguish between Type IIIb and IIIc SMA with Type IIIc being defined as when symptoms develop after 12 years but before 19 years, although Type IIIb is commonly used to describe onset of SMA symptoms from after 3 years to 18 years of age.
SMA = spinal muscular atrophy
Source: Table 1.1, page xviii of the resubmission

4.3 Nusinersen is an antisense oligonucleotide that increases the proportion of exon 7 inclusion in SMN2 messenger ribonucleic acid (mRNA) transcripts by binding to SMN2

pre-mRNA, thus increasing the level of SMN protein. Nusinersen is delivered intrathecally, directly into the cerebrospinal fluid, with or without image guidance. Four loading doses are given (days 0, 14, 28 and 63) and then maintenance doses are administered once every 4 months.

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

5 Comparator

5.1 The resubmission nominated standard of care (for no treatment) as the main comparator. This nomination was based on the absence of an alternate disease-modifying therapy available on the PBS for the treatment of adults with SMA (as of February 2021); however, the resubmission acknowledged that two new treatments for SMA (risdiplam and onasemnogene abeparvovec) are currently proceeding through registration and reimbursement processes.

5.2 The previous resubmissions (July 2021 and November 2020) also presented standard of care as the main comparator for adults with SMA. The PBAC previously considered that standard of care was an appropriate comparator (paragraph 7.5, p.33 nusinersen Public Summary Document [PSD], November 2020).

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 addressed the expectations of adults around treatment effectiveness, when to stop therapy, and the place of PROs in guiding treatment decisions as discussed in patient focus groups. In addition the clinician discussed the clinical outcomes and experience of 11 adult SMA patients treated with nusinersen.

6.2 In focus groups for adults living with SMA, key themes were the high prevalence of health related anxiety and fear with regard to functional decline and grief for functions that have been lost. Adults living with SMA reported that what constitutes treatment effectiveness in clinical trials (e.g. 6MWT) does not necessarily reflect priorities for patients for whom maintenance of independence and existing levels of function are valued more highly.

6.3 The clinician noted that for adults, the benefits of treatment with nusinersen are becoming apparent and the overall experience is positive, with some patients experiencing notable improvements in function. However for some patients the treatment burden for medication administration is too high to continue treatment and some patients experience lumbar puncture headaches. As such it is not expected

that all adults with SMA will take up treatment with nusinersen, nor will they continue indefinitely.

6.4 The clinician noted that patient focus groups included discussions of when to stop treatment. Patients were pragmatic and recognised the need to have criteria to guide continuation of treatment. Many patients felt that objective scores (HFMSE, RULM) didn't reflect all significant changes but changes in these scores are likely to reflect real changes (gain or decline). Patients expressed the view that if important functions remain then treatment should be continued, especially if scores had initially improved and not yet declined below baseline. The clinician stated that in addition to motor score assessments (HFMSE and RULM), continuing treatment restrictions should require patients and clinicians to establish an agreement that treatment is continuing to produce a worthwhile benefit using the PRO measures as a guide to the consultation and with consideration of quality of life taken into consideration. The clinician noted that neurologists are well trained in having these conversations about treatments and considered that assessment at 6-12 month intervals would be reasonable and 2 years would be adequate time for an individual to determine if they were benefiting from treatment.

6.5 The clinician noted that SMA treatment guidelines are progressing, with the final draft expected to be reviewed and endorsed in May. The Clinician also noted that work with physiotherapists has begun to enable motor function assessment to be conducted outside the hospital setting.

6.6 The PBAC considered that the sponsor hearing was informative, particularly in terms of the patient and clinician perspectives on meaningful outcomes for adults with SMA. The PBAC considered that the extensive consultation with patients was beneficial in informing the criteria for continuation of treatment.

Consumer comments

6.7 The PBAC noted that the results of patient focus group interviews facilitated by neurologists were provided via the consumer comments facility on the PBS website. These comments were consistent with the clinician's comments provided in the sponsor hearing. The report made the following recommendations:

- Treatment effectiveness should be determined using information from a combination of validated physical assessments, patient reported outcome measures and consultation between the adult living with SMA and the neuromuscular specialist. Effectiveness can be defined as improvement, stabilisation or minimal decline in symptoms over 2 years.
- Sustained or rapid decline in objective measures of SMA symptoms over 2 years should prompt a formal discussion between the adult living with SMA and the neuromuscular specialist to consider stopping treatment with nusinersen.
- Removal of the age restriction on the existing PBS indication for nusinersen to facilitate equitable access to treatment for all adults living with SMA.

6.8 The report noted that patients recognized that deciding when to stop treatment is a challenging situation and felt that decline in function alone was not sufficient to conclude treatment ineffectiveness and that both speed and the nature of decline should be evaluated. A concern with relying only on the physical assessment scores was the impact that a "bad day" or fatigue could have on performance and therefore patients considered that there should be reproducible evidence of decline in function over more than one assessment time period before a decline could be confirmed. In addition, assessment should include multiple sources of information (validated physical assessments, PROs and the opinions of both the adult with SMA and the treating neurologist). Patients felt that, given the burden of treatment administration, most adults would not choose to continue receiving nusinersen if they were not perceiving the treatment to be beneficial. It was felt that there should be ongoing assessments following cessation and that if a more rapid deterioration became apparent then that would be considered evidence of previous treatment effectiveness and recommencement of therapy could be considered.

6.9 The PBAC also noted and welcomed the input from individuals (51), health care professionals (2) and consumer groups (2) via the Consumer Comments facility on the PBS website.

6.10 Health professionals caring for people living with SMA noted the slow decline in function that leads to significant disability and burden for carers. Healthcare professionals noted that nusinersen has the potential to slow disease progression.

6.11 Patients who have accessed nusinersen via compassionate access programs noted improvements including in motor function such as sitting and standing, sleep, balance, strength, independence and a reduction in fear and anxiety around their future. Patients noted the value of maintaining their current level of function, strength and independence. Most patients noted that treatment administration was comfortable and any side effects were manageable. One patient reported they had experienced a CSF leak due to the lumbar puncture procedure.

6.12 Patients living with SMA who do not have access to treatment noted the decline in function over time, fatigue, falls resulting in broken bones and the inability to live independently and continue work, hobbies or caring roles. Patients noted that even small or subtle improvements and maintenance of finger strength or swallowing for eating and talking are valued by patients because of their impact on independence. Patients noted that there were currently no treatments that can slow or cease progression of SMA and noted the impact on their mental health. Patients expressed frustration that they have had to wait for access to treatment with nusinersen.

6.13 Other interested individuals noted that the clinical need is very high for adults with SMA, while patients less than 18 years or younger have had access for some time. They also noted that the cost of treatment is prohibitively high without PBS subsidisation.

Clinical trials

6.14 No head-to-head trials of nusinersen versus standard of care were available in adult patients with SMA.

6.15 Data for nusinersen in adults with SMA was informed by nine real-world studies (Maggi 2020, Hagenacker 2020, Walter 2019, Duong 2021, De Wel 2020, Jochmann 2020, Veerapandiyan 2019, Yeo 2020 and Elsheikh 2021a). Of these, eight studies were previously considered by the PBAC in July 2021, with one new nusinersen study (Elsheikh 2021a, n=19) included. One additional nusinersen study (Elsheikh 2021b) was identified during the evaluation.

6.16 For the comparator, nine real-world natural history studies were identified (Mercuri 2016, Montes 2018, Pera 2019, Coratti 2020a, Coratti 2020b, Wijngaarde 2020, Mazzone 2013, Sivo 2015 and Kaufmann 2011). Of these, two new studies (Kaufmann 2011, n=65 and Sivo 2015, n=74) were included. It was noted that Kaufmann 2011 was previously excluded because it was determined to be the wrong population (not all patients were adults) and therefore there may be applicability issues to the current resubmission, but it was unclear why Sivo 2015 was not identified previously by the resubmission or during evaluation.

6.17 The majority of the included clinical data has been reviewed by the PBAC previously. The approach to clinical evidence synthesis used in the resubmission relied on the evidence presented in the sponsors' regulatory submission to the European Medicines Agency (EMA) for nusinersen in adults with SMA, lodged in June 2021. The EMA submission provided an updated systematic literature review (SLR) of nusinersen and the natural history of adult patients with SMA. Meta-analyses for HFMSE, RULM and 6MWT from the EMA submission were presented in the resubmission. However no comparisons with the standard of care (from natural history studies) were presented.

6.18 Details of the studies presented in the resubmission are provided in Table 4.

Table 4: Studies and associated reports presented in the resubmission

Study ID	Protocol title/ Publication title	Publication citation
Non-randomised studies of treatment with nusinersen in adult patients		
Maggi 2020	Nusinersen safety and effects on motor function in adult spinal muscular atrophy type 2 and 3.	Journal of Neurology, Neurosurgery and Psychiatry 2020;91(11):1166-1174.
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.
Duong 2021	Nusinersen Treatment in Adults with Spinal Muscular Atrophy.	Neurology: Clinical Practice 2021; pp.10.1212/CPJ.0000000000001033.
Walter 2019	Safety and Treatment Effects of Nusinersen in Longstanding Adult 5q-SMA Type 3 – A Prospective Observational Study."	Journal of Neuromuscular Diseases 2019; 6(4): 453-465.
	P.354Treatment effects of nusinersen in longstanding adult 5q-SMA type 3 – a prospective observational study over 10 months.	Neuromuscular Disorders 2019; 29: S185.
De Wel 2020	Nusinersen treatment significantly improves hand grip strength, hand motor function and MRC sum scores in adult patients with spinal muscular atrophy types 3 and 4.	Journal of Neurology 2020;268(3):923-935.

Study ID	Protocol title/ Publication title	Publication citation
	THERAPY: P.279 Efficacy and safety of nusinersen treated adult patients with spinal muscular atrophy (SMA) types 2-3-4.	Neuromuscular Disorders. 2020;30:S128.
Jochmann 2020	Experiences from treating seven adult 5q spinal muscular atrophy patients with Nusinersen.	Therapeutic Advances in Neurological Disorders 2020;13, p.175628642090780.
Yeo 2020	Prospective Cohort Study of Nusinersen Treatment in Adults with Spinal Muscular Atrophy	J Neuromuscul Dis. 2020;7(3):257-268.
	Outcome measures for nusinersen efficacy in adults with spinal muscular atrophy.	Neurology 2019;92(15):S5.008.
Veerapandiyan 2019	Nusinersen for older patients with spinal muscular atrophy: A real-world clinical setting experience.	Muscle Nerve 2020;61(2):222– 226.
	Intrathecal nusinersen in older children and adults with spinal muscular atrophy.	Neurology 2019;92(15).S5.001.
Elsheikh 2021a	Safety, tolerability, and effect of nusinersen in non-ambulatory adults with spinal muscular atrophy.	Front. Neurol. 12:650532.
Nusinersen studies identified during the commentary		
Elsheikh 2021b	Safety, tolerability, and effect of nusinersen treatment in ambulatory adults with 5q-SMA	Front. Neurol. 12:650535
Natural history of SMA studies identified in updated SLR		
Coratti 2020a	Clinical Variability in Spinal Muscular Atrophy Type III.	Annals of Neurology. 2020;88(6):1109-1117. 10.1002/ana.25900
Coratti 2020b	Age and baseline values predict 12 and 24-month functional changes in type 2 SMA.	Neuromuscular Disorders. 2020;30(9):756-764. 10.1016/j.nmd.2020.07.005
Wijngaarde 2020a	Muscle strength and motor function in adolescents and adults with spinal muscular atrophy	Neurology. 2020;95(14):e1988-e1998. 10.1212/WNL.0000000000010540
Pera 2019	Revised upper limb module for spinal muscular atrophy: 12 month changes	Muscle and Nerve 2019: 59(4): 426-430.
Montes 2018	Ambulatory function in spinal muscular atrophy: Age-related patterns of progression	PloS ONE 13(6): e0199657
Mercuri 2016	Patterns of disease progression in type 2 and 3 SMA: Implications for clinical trials	Neuromuscular Disorders 2016: 26(2): 126-131.
Mazzone 2013	Six minute walk test in type III spinal muscular atrophy: A 12month longitudinal study	Neuromuscular Disorders 23(8): 624-628.
Kaufmann 2011	Observational study of spinal muscular atrophy type 2 and 3: functional outcomes over 1 year	Arch Neurol Jun;68(6):779-86.
Sivo 2015	Upper limb module in non-ambulant patients with spinal muscular atrophy: 12 month changes	Neuromuscular Disorders 25:212–215.

SLR = systematic literature review; SMA = spinal muscular atrophy
Source: Table 2.1, page li of the resubmission and Table 2.4, page 64 of the resubmission
Gray shaded cells indicate studies presented in July 2021 resubmission.

6.19 The key features of the included studies are summarised in Table 5.

Table 5: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias*	Patient population	Outcome(s)	Use in modelled evaluation
Nusinersen studies included in the SLR						
Maggi 2020	116	Retrospective cohort study single arm, 14 months	High	Type II and III SMA	HFMSE, RULM, 6MWT	HSFME, RULM and 6MWT responder rates, baseline age
Hagenacker 2020	124	Prospective, observational cohort study, single arm, 14 months	High	Type II and III SMA	HFMSE, RULM, 6MWT	Discontinuation rate used, baseline age
Duong 2021	42	Prospective observational study, single arm, mean treatment duration 12.5 months	High	Type II and III SMA	HFMSE, RULM, 6MWT	Not used
Walter 2019	19	Prospective, observational, single-arm, 10 months	High	Type III SMA	HFMSE, RULM, 6MWT	Not used
De Wel 2020	16	Prospective observational cohort study and retrospective study of natural history data,14 months	High	Type III and IV SMA	HFMSE, RULM, 6MWT	Not used
Jochmann 2020	7	Prospective case series, 10 months	High	Type II and III SMA	HFMSE, RULM, 6MWT	Not used
Yeo 2020		Prospective cohort study Mean 17 months	High	Type III SMA	HFMSE, RULM, 6MWT	Not used
Veerapandiyan 2019	12	A retrospective cross-sectional study Mean 17.4 months	High	Type III SMA	RULM	Not used
Elsheikh 2021a	19	Prospective observational; single arm, 14 months	High	Type II and III SMA	FVC, HFMSE, SMAFRS, RULM	Not used
Nusinersen studies identified during the commentary						
Elsheikh 2021b	13	Prospective observational; single arm, 14 months	High	Type III (12) and IV (1) SMA	MVICT, 6MWT, FVC, HFMSE, SMAFRS	Not used
Natural history of SMA studies identified in updated SLR						
Mercuri 2016	268	Natural history data	High	Type II and III SMA	HFMSE	Not used
Montes 2018	73		High	Type II sitters to Type IIIb SMA	6MWT	Not used
Pera 2019	108		High	Type II to Type III SMA	RULM	Not used
Coratti 2020a	182		High	Type III SMA	HFMSE	Not used
Coratti 2020b	267		High	Type II SMA	HFMSE	Not used
Wijngaarde 2020a	250		High	Type 1c to IV SMA	HFMSE	Not used
Mazzone 2013	38		High	Type III SMA	6MWT	Not used
Kaufmann 2011	65	Natural history data	High	Type II and III SMA	HFMSE, HFMS, GMFM	Not used
Sivo 2015	74		High	Type II and III SMA	HFMSE, ULM	Not used

GMFM = Gross Motor Function Measure; HFMS=Hammersmith Functional Motor Scale; HFMSE=Hammersmith Functional Motor Scale–Expanded; 6MWT=6 min walking test; NR=not reported; MVICT = Maximal Voluntary Isometric Muscle Contraction Testing; RULM=Revised Upper Limb Module; SLR = systematic literature review; SMA=spinal muscular atrophy, SMAFRS = modified SMA function rating scale; ULM = Upper Limb Module

* The risk of bias which was assessed using the ROBINS-1 tool for nonrandomised studies.

Cells shaded grey represent studies presented in the nusinersen November 2020 resubmission.

Source: Compiled from Section 2 of the previous resubmission (July 2021), Elsheikh 2021a, Elsheikh 2021b, Kaufmann 2011 & Sivo 2015.

6.20 None of the included nusinersen studies, including Elsheikh 2021a and Elsheikh 2021b which were new to the resubmission, provided data beyond 14 months of treatment.

6.21 The nusinersen studies were considered to have a high risk of bias, as they were open label, non-comparative and non-randomised studies. For similar reasons, the natural history studies were also considered to have a high risk of bias due to the lack of matching comparison, lack of blinding and likely selection bias (as patients selected for retrospective studies were selected based on available data).

6.22 As in previous resubmissions (July 2021 and November 2020), the current resubmission proposed that a ≥3 point change in HFMSE, or a ≥2 point change in RULM, or a ≥30 metres change in 6MWT were considered clinically meaningful. The ESC has previously 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 wheelchair) and that, for many non-ambulant patients, mobility in terms of transfer movements in and out of chairs was clinically meaningful (paragraph 6.23, p13 nusinersen PSD, November 2020).

6.23 As discussed in paragraph 3.5, the proposed nusinersen restriction included assessment of fine motor function which was to be assessed using the patient reported outcome measures SMA-HI and SMAFRS motor function. The SMA-HI is a patient-reported outcome that aims to measure an SMA patient's perception of their disease burden by measuring 15 areas of SMA health (hip, thigh and knee function, shoulder and arm function, social performance, fatigue, activity participation, hand and finger strength, social satisfaction, emotional health, pain, breathing function, swallowing function, sleep, gastrointestinal function, mobility and ambulation). The SMAFRS is an ordinal rating scale based around 10 aspects of activities of daily living – eating, dressing upper body, dressing lower body, bathing, toileting, grooming and oral hygiene, turning in bed, transfers, walking, climbing stairs. Each subset scored from 0 (fully dependent) to 5 (fully independent) by the patient or caregiver. Inappropriately, no clinical evidence for SMA-HI or SMAFRS was provided in the resubmission. SMA-HI results were not reported in any of the included studies, and results using the SMAFRS were reported by Duong 2021, Yeo 2020, Elsheikh 2021a and Elsheikh 2021b. The PBAC has not considered either SMAFRS or SMA-HI in treatment for SMA in previous (re)submissions.

Comparative effectiveness

6.24 The individual efficacy results for HFMSE from the nusinersen studies and natural history studies are presented in Table 6.

Table 6: HFMSE change from baseline across published studies

Study	Type	N	Mean Age in years (SD)	Mean Baseline HFMSE (SD)	Annualised change from baseline (mean (SD); median (range)), p-value
Nusinersen studies					
Maggi 2020[a]	Type II + III (All)	51	36.8 (13.3), n=116	26.5 (21.7), n=116	+5.38 (NR); +8.5 (NR)
	Non-ambulatory Type II	5	26.3 (7.5), n=13	1.46 (2.82), n=13	+1.2 (2.68); 0 (0 to 6), p>0.05
	Non-ambulatory Type III sitters	19	40.8 (14.0), n=51	11.41 (9.6), n=51	+3.53 (3.67); +3 (-3 to 11), p=0.0014
	Ambulatory Type III walkers	27	35.5 (12.2), n=52	47.56 (11.3), n=52	+2.37 (2.22); +2 (-2 to 6), p=0.00016
Hagenacker 2020[a]	Type II + III (All)	57	33 (11)	24.7 (21.8)	+3.12 (4.02); NR (2.06 to 4.19), p<0.0001
	Type II	19	28.9 (9.41)	4.8 (8.5)	+1.1 (1.4); 0 (0.4 to 1.7) p=0.0059
	Type III	38	35.7 (11.6)	34.6 (19.5)	+4.2 (4.5); 3 (2.7 to 5.7) p<0.0001
Hagenacker 2020[a] (subgroup analysis)	Ambulant patients	23	NR	NR	+4.6 (4.4); NR (NR), p<0.0001
	Non-ambulant patients	34	NR	NR	+2.1 (3.4); NR (NR), p<0.0001
Duong 2021	Type II + III (All)	31	33.7 (NR) n=42	Median 19 (range 0- 60) n=42	+0.86 (95%CI -0.52 to 2.24); NR (NR)
	Type II	11			+0.66 (95%CI -1.63 to 2.95); NR (NR)
	Type III	20			+0.99 (95%CI -0.77 to 2.74); NR (NR)
	Non-sitter	9			-0.24 (95%CI -3.57 to 3.09); NR (NR)
	Sitter	11			+1.13 (95%CI -1.11 to 3.36); NR (NR)
	Walker	11			+1.09 (95%CI -1.26 to 3.44); NR (NR)
Walter 2019[b]	Type III (All)	19	35.2 (11.7)	35.16 (21.1)	+4.34 (NR); NR (NR) p=0.201
De Wel 2020[a]	Type III (n=14) + IV (n=2) (All)	16	Median 37.5 (range 22-66)	27.3 (19.8)	+2.1 (NR); NR (NR) p=0.31
Jochmann 2020[b]	Type II and III	6	41.2, N=7	13.9 (NR)	+5 (6.5); NR (NR)
Yeo 2020[a]	Type III	6	Median 29.9 (range 24.9-65.5)	Median 35 (range 21, 53)	+2 (NR); NR (1 to 5)
Elsheikh 2021a[l]	Type II (9) + III (10) (All)	19	39.7 (13.9) (range 21.3-64.8)	3.47 (5.7) (range 0.1-6.93)	+0.11 (95% CI: -1.11 to 1.32); NR; p=0.8606[m]

Study	Type	N	Mean Age in years (SD)	Mean Baseline HFMSE (SD)	Annualised change from baseline (mean (SD); median (range)), p-value
Elsheikh 2021b	Type III (12) + IV (1) (All)	13	36.6 (NR) (range 18-58)	45.85 (NR) (range 23-59)	+2.6 (95% CI 0.5 to 4.69), NR; p=0.0165[m]
Natural history studies					
Mercuri 2016	Type II	17	26.6 (7.5)	4.84	-0.059[c] (NR); NR (NR)
	Type III[c]	12	29.4 (12.9)	55.2	-0.17[c] (NR); NR (NR)
Wadman 2018	Type IIa	44[e]	15-30	1.93[d]	-0.129 (NR); NR (NR)
			30+	0.00[d]	0.000[f] (NR); NR (NR)
	Type IIb	36[e]	15-30	6.09[d]	-0.030 (NR); NR (NR)
			30+	NR	-0.165 (NR); NR (NR)
	Type IIIa	40[e]	15-30	30.74[d]	-1.643 (NR); NR (NR)
			30+	NR	-0.085 (NR); NR (NR)
	Type IIIb	36[e]	15-30	64.9[d]	-1.178 (NR); NR (NR)
			30+	NR	-0.940 (NR); NR (NR)
Coratti 2020a[g]	Type III (>20y)	49	23.99 (2.67)	30.42 (18.70)	-1.65 (3.42); NR (NR)
	Ambulant	18	23.67 (2.94)	51.94 (7.63)	-1.56 (3.96); NR (NR)
	Non-ambulant	31	24.19 (2.53)	17.93 (9.38)	-1.70 (3.14); NR (NR)
	Type IIIa (>20y)	27	24.18 (2.24)	23.07 (17.47)	-2.18 (3.54); NR (NR)
	Ambulant	8	24.45 (1.66)	47.63 (6.12)	-3.25 (4.89); NR (NR)
	Non-ambulant	19	24.07 (2.48)	12.74 (6.77)	-1.74 (2.84); NR (NR)
	Type IIIb (>20y)	22	23.77 (3.16)	39.45 (16.34)	-1.00 (3.24); NR (NR)
	Ambulant	10	23.04 (3.63)	55.40 (7.14)	-0.20 (2.53); NR (NR)
	Non-ambulant	12	24.38 (2.73)	26.17 (6.66)	-1.67 (3.70); NR (NR)
Coratti 2020b	Type II (all)	652[j]	9.41 (6.32)	11.55 (9.24)	-0.68 (3.28); NR (-13 to +12)
	Type II (>13yr)	117	20.21 (5.75)	3.21 (3.79)	-0.26 (1.37); NR (-10 to 3)
	Type II (>18y)[h]	54	24.24 (5.10)	NR	-0.15 (1.28); NR (NR)
Wijngaarde 2020a[i]	Type IIa	68	13.4 (5.9-21.2)	9.27 (1.09)	−0.29 (95%CI -0.39, -0.18); NR (NR)
	Type IIb	50	15.0 (7.0-24.7)	20.58 (2.07)	−0.46 (95%CI -0.61, -0.30); NR (NR)
	Type IIIa	63	25.2 (6.2-47.6)	44.53 (2.74)	−0.73 (95%CI -0.88, -0.58); NR (NR)
	Type IIIb	40	42.8 (26.7-48.3)	60.01 (7.06)	−0.56 (95%CI -0.93, -0.19); NR (NR)
Kaufmann 2011	Type II and III	48	11.2 (9.1)[k]	20.1 (15.5)[k]	0.15 (3.22); NR (NR)
Sivo 2015	Type II (70) and III (4)	74	10.22 (6.15)	12.43 (9.13)	-0.35 (range -5 to 5); NR (NR)

CI = confidence interval; HFMSE=Hammersmith motor function scale – expanded; NR=not reported; SD=Standard deviation; SMA=spinal muscular atrophy

[a]Data reported for patients who had 14 month assessment only. Baseline values include all patients enrolled.

[b]Data represents 10 month assessment expressed. Mean age of patients and baseline HFMSE in Jochmann 2020 recalculated during evaluation.
[c]Derived from Mercuri Figure 1 in patients ≥18; change over 12 months. The resubmission excluded the one patient aged 17.64.
[d] Visually extracted according to resubmission. However these baseline values appear to be of those aged between 10-19.9 years according to Attachment 2 to the resubmission. These values could not be independently verified during evaluation.
[e]Age group sizes not reported, consequently, the N presented here includes patients across all ages for each SMA type.
[f]Change of zero due to a mean of zero in this patient group.
[g]12 month changes reported for the >20 subgroup in supplementary table 1.
[h]Estimates are based on IPD (not defined by resubmission) analysis extracted from figure 2 of source document (Nb. Overlapping data points, particularly at 0 change means that not all data points may have been captured in analysis).
[i]Baseline and annualised change in HFMSE are based on intercept (SE) and slope from model parameter estimates as reported in table 2 of source document.
[j] 652 12 month assessments taken from 267 patients (150 males and 117 females)
[k] Baseline data for all participants, n=65
[l] In the Elsheikh 2021a study, due to phenotype severity, HFMSE scores were scorable in only six patients and were scored as 0 in the other patients (floor effect) (N=19).
[m]Change from baseline results for 14 months follow up.
Cells shaded grey represent studies presented in the nusinersen July 2021 resubmission. Text in italics indicate values extracted during evaluation.
Source: Table 2.2, p lii of the resubmission, 2.80, p255 of the July resubmission, Elsheikh 2021a, Elsheikh 2021b. Kaufman 2011 and Sivo 2015

6.25 The newly identified nusinersen studies (Elsheikh 2021a and 2021b) both reported HFMSE change from baseline. The magnitude of change from baseline reported was similar to other nusinersen studies.

6.26 HFMSE results were reported for the two newly identified natural history studies. The resubmission noted HFMSE scores decreased an average of 0.35 points (Sivo 2015) over a 12-month period in untreated patients with SMA Types II and III. Kaufmann 2011 reported no significant change in mean HFMSE scores over a 12-month period (mean change: 0.15; SD: 3.22) among patients with SMA Types II and III (n = 48). Of the 65 patients included in the dataset, only 32% of them were at least 12 years of age at baseline limiting the applicability of the study to adult the population. Kaufman 2011 attributed the motor function improvements in ambulatory patients to the learning effect or delayed developmental gain in younger children (i.e., ambulatory participants <5 years), arguing that it was in part associated with developmental gain of motor milestones in children who walk relatively late because of their underlying condition. The mean rate of HFMSE changes was –0.47 (95% CI: –1.66 to 0.72) in non-ambulatory participants.

6.27 Comments by the PBAC at the July 2021 meeting regarding efficacy results remain applicable to the current resubmission, given that largely the same studies were included. The PBAC previously observed the following regarding the studies reporting change in HFMSE:

- The results for all patients in Maggi 2020 may be uncertain due to inconsistencies between the values reported in the publication and in the published supplementary data (paragraph 6.20, nusinersen PSD, July 2021 PBAC meeting).
- Apart from Maggi 2020, the included nusinersen studies report that adult patients with Type II or III SMA treated with nusinersen experienced a mean annualised

HFMSE improvement from baseline between 0.66 to 4.6 points based on a mean period of 10 to 14 months of treatment (six to seven doses), but a number of patients may continue to experience motor function decline. The natural history study data suggested that HFMSE may remain stable or decline in adult patients without treatment (mean annualised change from baseline ranging from 0.00 to – 3.25), although some patients may experience an improvement from baseline (e.g. Coratti 2020b reported that 11.0% and 9.5% of patients showed an improvement in HFMSE of >2 points after 12 months and 24 months, respectively) (paragraph 6.21, nusinersen PSD, July 2021 PBAC meeting).

6.28 The individual efficacy results for RULM from the nusinersen studies and the natural history studies are presented in Table 7.

Table 7: RULM change from baseline across published studies

Study	Type	N	Mean Age in years (SD)	Mean Baseline RULM (SD)	Annualised change from baseline (mean (SD); median (range)) – p-value
Nusinersen studies					
Maggi 2020[a]	Type II + III (All)	50	36.8 (13.3), n=116	25.2 (11.6), n=114	+2.4 (NR); +1.5 (NR)
	Non-ambulatory Type II	5	26.3 (7.5), n=13	6.42 (8.4), n=12	+1.6 (1.52); 2 (0 to 3), P>0.05
	Non-ambulatory Type III sitters	19	40.8 (14.0), n=51	20.16 (8.6), n=51	+1.47 (2.5); 2 (-6 to 5), p=0.018
	Ambulatory Type III walkers	25	35.5 (12.2), n=52	34.71 (36), n=51	+0.4 (1.83); 0 (-3 to 6), P>0.05
Hagenacker 2020[a]	Type II + III (All)	57	33 (11)	23.85 (12.16), n = 58	+1.09 (±1.75); NR (0.62 to 1.55) p<0.0001
	Type II	19	28.9 (9.41)	12.3 (9.0)	+1.6 (±2.0); NR (0.7 to 2.5) p=0.0049
	Type III	38	35.7 (11.6)	29.5 (9.1)	+0.7 (±1.7); NR (0.2 to 1.3) p=0.01
Duong 2021	Type II + III (All)	39	33.7 (NR) n=42	18.2 (range 0-37) n=42	+0.11 (95%CI -0.45, 0.67); NR (NR)
	Type II	16			+0.43 (95%CI -0.44, 1.31); NR (NR)
	Type III	23			-0.12 (95%CI -0.81 to 0.57); NR (NR)
	Non-sitter	16			-0.17 (95%CI -1.09 to 0.74); NR (NR)
	Sitter	12			+0.74 (95%CI -0.32 to 1.80); NR (NR)
	Walker	11			-0.01 (95%CI -1.02 to 0.99); NR (NR)
Walter 2019[b]	Type III (All)	19	35.2 (11.7)	32.32 (7.39)	+0.74 (0)p=0.048
De Wel 2020[a]	Type III + IV (All)	16	Median 37.5 (range 22-66)	27.1 (8.10)	+1.06 (95%CI-0.79 to 2.91); NR (NR) p=0.24
Jochmann 2020	Type II and III	6	41.2, N=7[e]	11.7 (NR)[e]	+7.7 (9.3); NR (NR)
Yeo 2020	Type III	6	Median 29.9 (range 24.9-65.5)	31.5 (range 22–37)	+1.8(NR); NR (0, 3), p < 0.05
Veerapandiyan 2019	Type I, II and III	4	35.8 (NR)N=4	16.7 (NR)	+1.6[d] (NR); NR (NR)
Elsheikh 2021a[f]	Type II (9) + III (10) (All)	19	39.7 (13.9) (range 21.3-64.8)	12.42 (11.5) (range 6.91-17.93)	+0.27 (95% CI: -0.96 to 1.5); NR; p=0.6637
Natural history studies					
Pera 2019 Patients ≥18 years[c]	All	24	NR (NR)	22.0 (NR)	-0.7 (2.5); NR (NR)
	Type II	11	NR (NR)	11.8 (NR)	+0.6 (1.9); NR (NR)
	Type III non-ambulant	6	NR (NR)	22.7 (NR)	-1.7 (2.4); NR (NR)
	Type III ambulant	7	NR (NR)	36.0 (NR)	-1.4 (2.7); NR (NR)

[a]Data represents 14 month assessment expressed. Baseline values include all patients enrolled.
[b]Data represents 10 month assessment expressed.

[c]Data extracted using DigitizeIT Software.
[d]Increase from baseline to last assessment. Last assessment varied from 9 to 26 months.
[e]Mean age of patients and baseline HFMSE in Jochmann 2020 recalculated during evaluation
[f] In the Elsheikh 2021 study, due to phenotype severity, RULM scores were scorable in only 13 patients (N=19). Change from baseline results for 14 months follow up.
Data shaded grey was presented in the nusinersen July 2021 resubmission.
CI = confidence interval; NR = not reported RULM = Revised upper limb module; SD = Standard deviation; SMA = spinal muscular atrophy
Source: Table 2.82, p259 of the July 2021 resubmission and Elsheikh 2021a

6.29 Among the newly identified studies, only Elsheikh 2021a reported RULM outcomes. Elsheikh 2021a reported RULM change from baseline results of +0.89 (95% CI: -0.16 to 1.95), +0.95 (95% CI: -0.1 to 2.0) and +0.27 (95% CI: -0.96 to 1.5) at 6, 10 and 14 months respectively, which was generally consistent with the other included nusinersen studies.

6.30 At their meeting in July 2021, the PBAC observed the following for the studies reporting change in RULM:

- The ambulant SMA Type III walkers in Maggi 2020 and Type III (All patients) in Walter 2019 both had a median baseline score of 37 points, which is the maximum possible score on the RULM scale. Patients then generally maintained this functionality for the duration of follow up. The resubmission reasonably reported that an observed ceiling effect indicated that RULM may not be sensitive enough to capture functional gains attributable to nusinersen treatment in this patient population (paragraph 6.27, nusinersen PSD, July 2021 PBAC meeting).
- Given the non-comparative nature of the data, limited amount of natural history data available with which to compare nusinersen data, the heterogeneity of the population, the inconsistencies in the follow up period of the nusinersen studies, the data inconsistencies observed with the Maggi 2020 study and the ceiling effect observed for the RULM outcome, it was difficult to draw any reliable conclusions from the available RULM data in the naïve comparison (paragraph 6.28, nusinersen PSD, July 2021 PBAC meeting).
- While the data appears to suggest that adult SMA patients treated with nusinersen experience a small increase or at least no decline in RULM scores, in the absence of a direct comparative study, it was not possible to elicit an incremental benefit for treatment with nusinersen compared to best supportive care. This was consistent with the PBAC's previous consideration that while a claim of superior comparative effectiveness of nusinersen to standard of care was reasonable, the magnitude and durability of benefit was not able to be quantified based on the data presented (paragraph 6.32, nusinersen PSD, July 2021 PBAC meeting).

6.31 The 6MWT results from the nusinersen studies and the natural history studies are presented in Table 8.

Table 8: Change in 6MWT from baseline across studies

Study	Type	N	Mean age in years (SD)	Mean baseline 6MWT metres (SD)	Annualised change from baseline (mean (SD); median (range)) – p-value
Nusinersen studies					
Maggi 2020[a]	Ambulatory Type III walkers	24	35.5 (12.2), n=52	308 (140), n=48	+23.11 (51.2); 20 (-101 to 111) p=0.016
Hagenacker 2020[a]	Type III	25	35.7 (11.6)	371.43 (210.34)[g]	+46.0 (49.91); 46 (25.4 to 66.6)[h] p<0.0001
Duong 2021	Walkers	10	33.7 n=42	300 (123.8) n=42	+3.29 (95%CI -28.04 to 34.62); NR (NR)
Walter 2019[b]	Type III (All)	11	35.2 (11.7)	369.5 (126.6)	+8.25 (NR); NR (NR) p=0.01
De Wel 2020[a]	Type III + IV (All)	7	Median 37.5	296 (199)	+7 (95%CI -38.42 to 53.27); NR (NR) p=0.71
Yeo 2020	Type III	4	Median 29.9 (range 24.9-65.5)	249 (range 74, 429)	NR [No results clinically or statistically meaningful.]
Elsheikh 2021b[a]	Type III + IV (All)	13	Median 36.6 (range 18-59)	262.88 (NR)	+15.88 (95% CI -2.16 to 33.92); NR (NR); p=0.0829
Natural history studies					
Montes 2018	Type III	15	>20 years	NR (NR)	-9.7 (NR); NR (-19.3 to -0.1), p=0.05
Querin 2021[c]	Type III + IV	14	43.5 (12.1)	341.3 (247.6)	-4 (NR); NR (NR) p=0.318 [i]
Mazzone 2013[d]	Type IIIa	2	>18 years	NR (NR)	+17.06 (NR); NR (NR)
	Type IIIb	6	>18 years	NR (NR)	+22.35 (NR); NR (NR)
Bonati 2017[e]	Type III	19	32 (13) (range 11-51)	460.05 (138.12) n=18	+38.88 (based on a final assessment of 498.93m available in 14 of 18 patients)

[a]Data represents 14 month assessment expressed
[b]Data represents 10 month assessment expressed
[c]Annualised change was estimated from mean baseline and 24 months values reported in Table 1 of Querin 2021.
[d]Estimates are based on IPD analysis extracted from figure 1a of source document.
[e]Previously excluded due to insufficient baseline data on underlying disease; not all patients were adults (the composition of group of patients by age is unclear), and no subgroup data presented.
[f]Jochmann 2020 reported 6MWT results for one patient only. This data has therefore not been included in the table.
[g]The result provided is the figure reported in the publication by Hagenacker 2020. The supplementary appendix to Hagenacker 2020 shows this result to be 356 (212.9).
[h]The result provided is the figure reported in the publication by Hagenacker 2020. The supplementary appendix to Hagenacker 2020 shows the median result to be 46 (0-71).
[i]Likely estimated as half the difference between the point estimate at baseline (341.3m) and at 24 months (333.3m)
CI = confidence interval; NR=not reported; 6MWT = six minute walking test; SD=Standard deviation; SMA=spinal muscular atrophy
Source: Table 2.84, p264 in the July 2021 resubmission and Elsheikh 2021b

6.32 Among the newly identified studies, only Elsheikh 2021b reported 6MWT outcomes. Elsheikh 2021b reported 6MWT change from baseline results of +25.27m (95% CI: 8.69 to 41.85), +19.19 (95% CI: 2.61 to 35.77) and +15.88 (95% CI: -2.16 to 33.92) at 6, 10 and 14 months respectively. This indicated that while improvements over baseline measures in the 6MWT were observed at all timepoints, the benefit appeared to decline over time.

6.33 In the July 2021 resubmission, the PBAC observed that the results reported in the resubmission for the 6MWT in the nusinersen studies were highly variable, ranging in

change from baseline from +7 metres (m) in De Wel 2020 to +46.0 m in SMA Type III patients in Hagenacker 2020. The 6MWT results for the natural history studies varied in a similar manner, ranging from -9.7 m (Montes 2018) to +38.88 m (Bonati 2017). The inconsistency between studies within the nusinersen and natural history studies made it difficult to draw any conclusions from the naïve comparison for the 6MWT outcome (paragraph 6.34, nusinersen PSD, July 2021 PBAC meeting).

6.34 The PBAC previously considered that nusinersen provides a minor added benefit, versus standard of care for adult patients with Type II and III SMA, which is clinically relevant. However, the PBAC considered that there was a low level of confidence in the clinical data in terms of identifying the patients most likely to benefit from treatment, the magnitude of the incremental benefit and durability of benefit. The PBAC considered that these factors remained uncertain and could not be determined from the available data. The PBAC noted there was heterogeneity within and across the nusinersen studies with respect to patient age, ambulation status, degree of disease progression and the extent of function at baseline. The PBAC considered that the naïve comparison with natural history studies indicated that treatment with nusinersen was associated with some improvement in outcomes however, the PBAC noted there was variability in the reported results within and between studies, particularly for the 6MWT outcome (paragraph 7.5, nusinersen PSD, July 2021 PBAC meeting). As only one additional nusinersen study and two additional natural history studies were identified in the resubmission which provided consistent results with existing studies and not providing any comparative data, these comments remain applicable to the current resubmission.

6.35 Table 9 provides a summary of the SMAFRS results for the four nusinersen studies reporting this outcome, however no nusinersen study reported SMA-HI as an outcome and none of the identified natural history studies reported either SMAFRS or SMA-HI.

Table 9: Change in SMA-FRS from baseline across studies

Study	Type	N	Mean age in years (range)	SMA-FRS (SD)	Annualised change from baseline, mean (95% CI) – p-value
Nusinersen studies					
Duong 2021	Walkers	42	33.7 (17.7-66.1)	15.0 (123.8)	1.44 (0.04 to 2.83), p=0.04
Yeo 2020	Type III	6	Median 29.9 (24.9-56.5)	31.5 (range 21, 37)	NR [a]
Elsheikh 2021a	Type II + III (All)	19	39.7 (13.9) (21.3-64.8)	11.16 (NR)	-0.98 (-2.1 to 0.13); p=0.1306[b]
Elsheikh 2021b	Type III + IV (All)	13	Median 36.6 (18-59)	31.23 (NR)	+1.57 (0.23 to 2.92); p=0.0224[b]

[a] Yeo 2020 did not provide median or mean results but reported that there was marked individual variability in activities of daily function as measured by the modified SMAFRS, with four participants reporting decline and two reporting stability or improvement.
[b] Change from baseline results for 14 months follow up.
CI = confidence interval; NR=not reported; SD=Standard deviation; SMAFRS = spinal muscular atrophy function rating scale
Source: Constructed during evaluation.

6.36 Based on the limited data available from small studies, perhaps reflecting the heterogeneity of the patient population, the results for nusinersen on SMAFRS were

inconsistent. Elsheikh 2021a (Type II and III SMA, n=19) reported a -0.98 annualised change (worsening) from baseline (although results were not statistically significant) but Duong 2021 (Walkers, n=42) and Elsheikh 2021b (Type III and IV SMA, n=13) reported statistically significant annualised change (improvement) from base line of +1.44-1.57 points. The baseline SMAFRS also varied significantly between studies and did not appear to be consistent with the type of SMA patients enrolled (e.g. Duong 2021 and Elsheikh 2021b both enrolled ambulatory patients but median baseline SMAFRS in Duong was 15.0 compared to a mean of 31.23 in Elsheikh 2021b). Overall, there does not appear to be sufficient evidence to indicate that nusinersen treatment has a positive effect on SMAFRS. No comparisons with natural history studies for SMAFRS was possible.

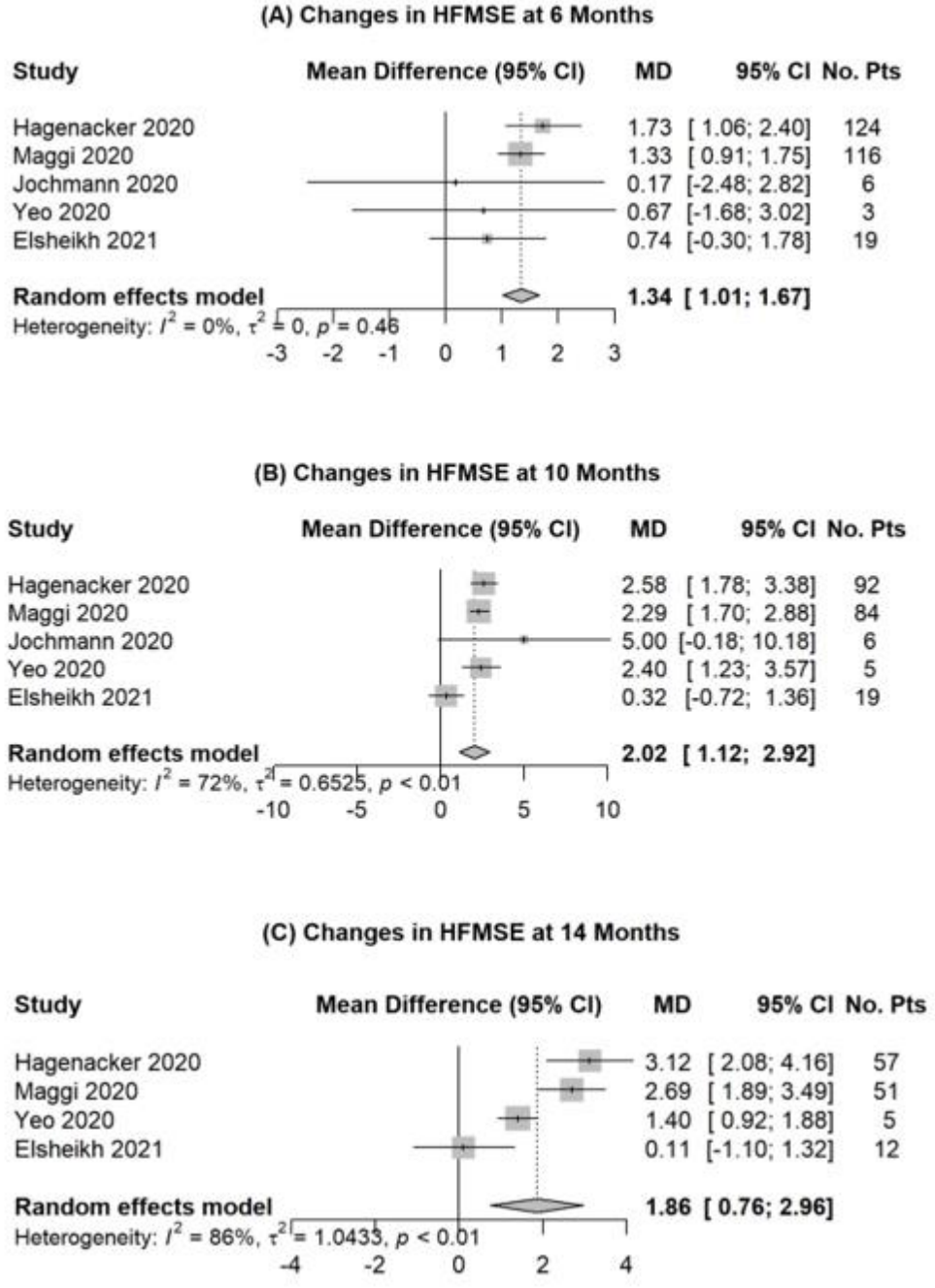
6.37 The resubmission reported that a meta-analysis was undertaken to provide a consolidated quantitative review of individual studies identified in the EMA report systematic literature review. For each motor function outcome (HFMSE, RULM, and 6MWT), the following were pooled across studies in the meta-analysis: (1) mean difference in motor function score from baseline (nusinersen initiation) to 6, 10, and 14 months of follow-up; and (2) percentage of patients with a clinically meaningful response during the same period defined as:

- ≥3 point change from baseline on the HFMSE;
- ≥2 point change from baseline in RULM;
- >30 metre change from baseline on the 6MWT.

6.38 The resubmission did not present information on the transitivity and comparability of the studies to justify their inclusion in a meta-analysis. In the evaluation of the previous resubmission (July 2021), the PBAC noted that the SMA patients included in the nusinersen studies were a highly heterogeneous population, with large variations in time of SMA onset, baseline motor functional scores and ambulatory status (paragraph 6.12, nusinersen PSD, July 2021 PBAC meeting), and the resubmission's results in the meta-analysis did not appear to have adjusted for multiple testing (results compared at 6, 10 and 14 months), therefore the confidence intervals and statistical significance of the values applied in the meta-analyses was uncertain and prone to bias. As such, the results of the meta-analyses presented should be interpreted with caution.

6.39 Figure 1 provides the meta-analyses results of the mean changes in HFMSE scores.

Figure 1: Mean Changes in HFMSE Scores From baseline to (A) 6 Months, 10 Months, and (C) 14 Months After Nusinersen Initiation - Overall Population

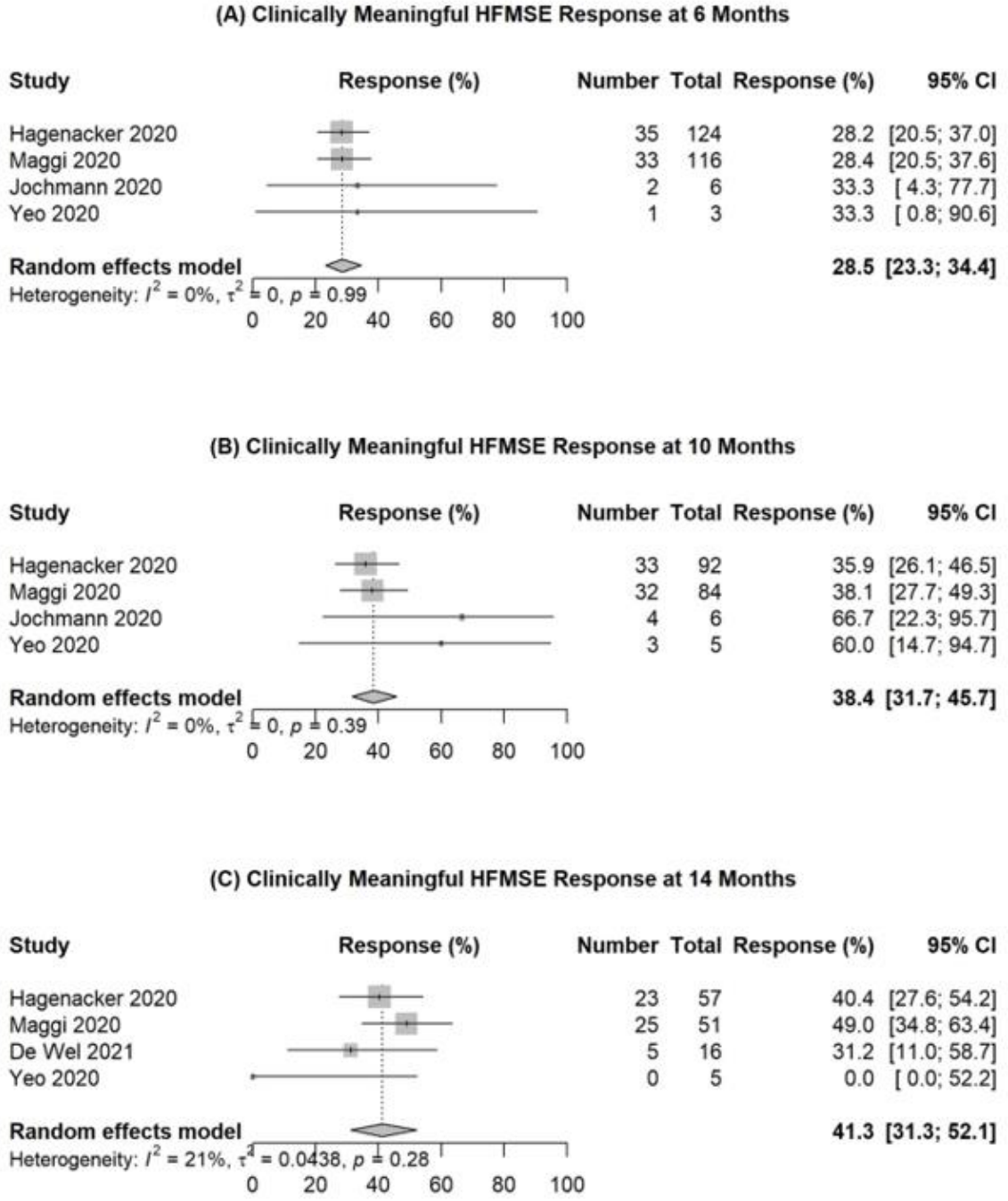


Source: Figure 2.1, page lvi of the resubmission

6.40 The results observed for the meta-analyses of mean change in HFMSE score all failed to meet the clinically meaningful difference for HFMSE as proposed by the resubmission (≥3 point change), at any of the six, 10 and 14 month time points.

6.41 Figure 2 provides the results of the meta-analyses of the percentage of patients with a clinically meaningful HFMSE response.

Figure 2: Percentage of Patients with Clinically Meaningful HFMSE Responses at (A) 6 Months, (B) 10 Months, and (C) 14 Months After Nusinersen Initiation - Overall Population



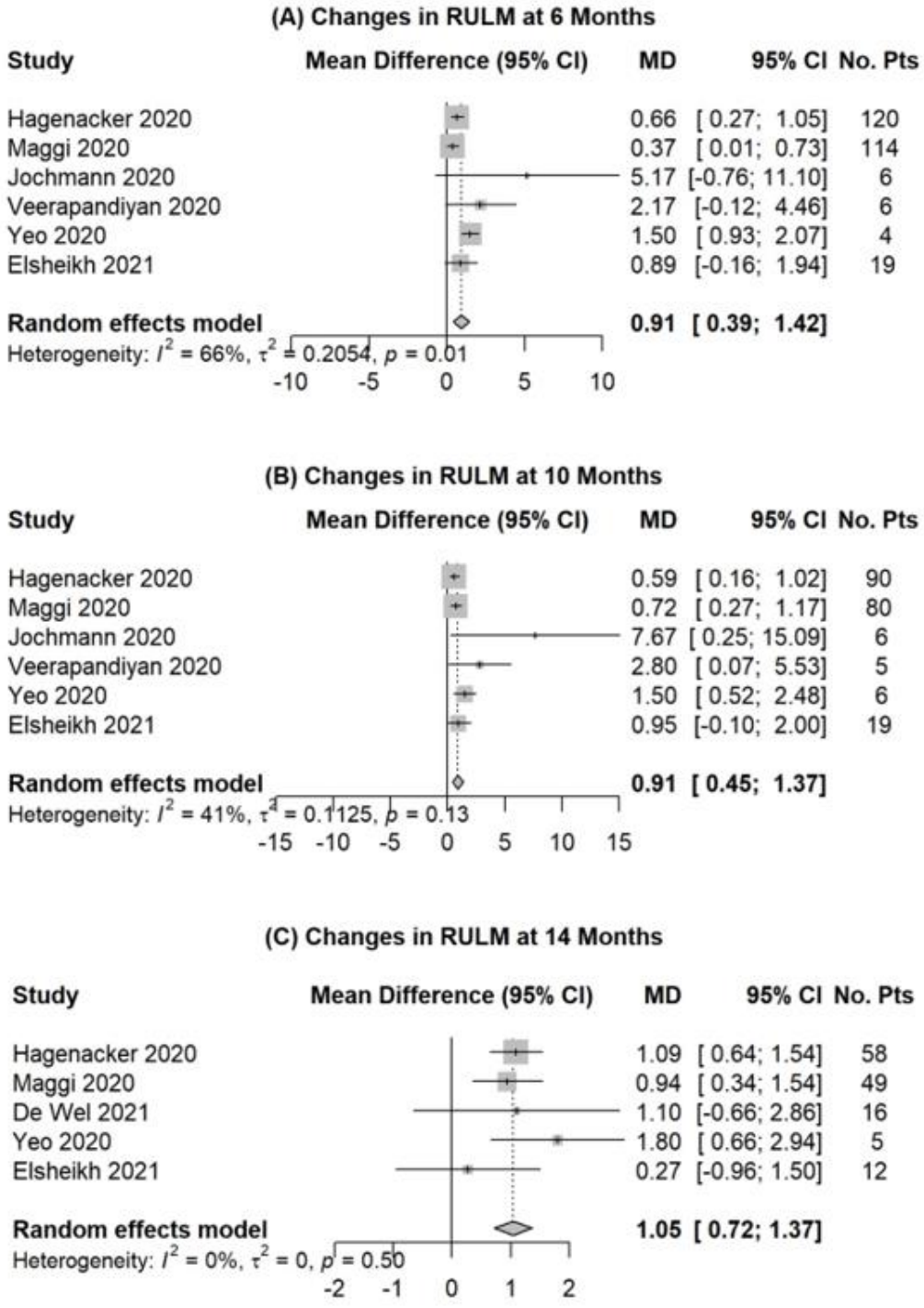
Source: Figure 2.2, page lvii of the resubmission

6.42 As noted in the consideration of the July 2021 resubmission (paragraph 6.39, nusinersen PSD, July 2021 PBAC meeting), the estimation of the proportion of responders in Maggi 2020, which reported that the proportion of responders

increased over time, was misleading because the total number of patients evaluated at each time point progressively decreased, likely because patients who were non-responders disproportionately were more likely to stop treatment, and that a more reasonable approach would be to use the same number of evaluable patients for all time points based on the number of patients enrolled (i.e. an intention to treat approach). Further, as no adjustments for multiple testing was considered, the significance (and by extension, the confidence interval) of each of the response rates at each time point was uncertain. These issues also apply to Hagenacker 2020, which demonstrated the same pattern of excluding non-responders from the denominator at 10 and 14 months, and given that the results of this meta-analysis were driven by both Maggi 2020 and Hagenacker 2020, the results should be interpreted with great caution.

6.43 The meta-analyses of the mean change in RULM scores are provided in Figure 3.

Figure 3: Mean Changes in RULM Scores From baseline to (A) 6 Months, (B) 10 Months, and (C) 14 Months After Nusinersen Initiation – Overall Population

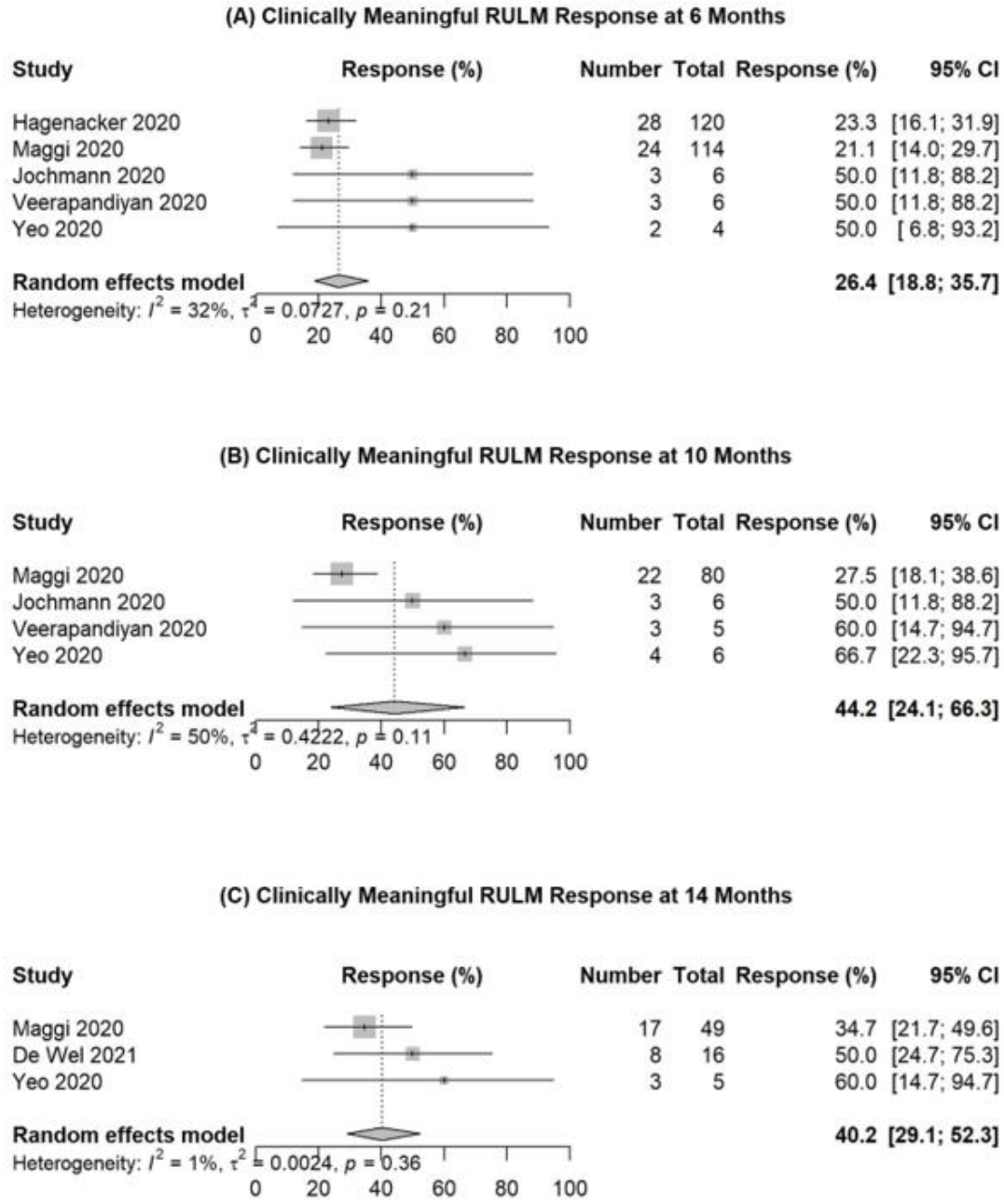


Source: Summary of clinical efficacy Figure 7 pg.65

6.44 The results of the meta-analysis of mean change in RULM score and its 95% confidence intervals all failed to meet the proposed clinically meaningful criteria (≥2 point change in RULM) at the six, 10 and 14 month time points.

6.45 Figure 4 provides the results from the meta-analyses of the percentage of patients with a clinically meaningful RULM response.

Figure 4:Percentage of Patients with Clinically Meaningful RULM Responses at (A) 6 Months, (B) 10 Months, and (C) 14 Months After Nusinersen Initiation - Overall Population

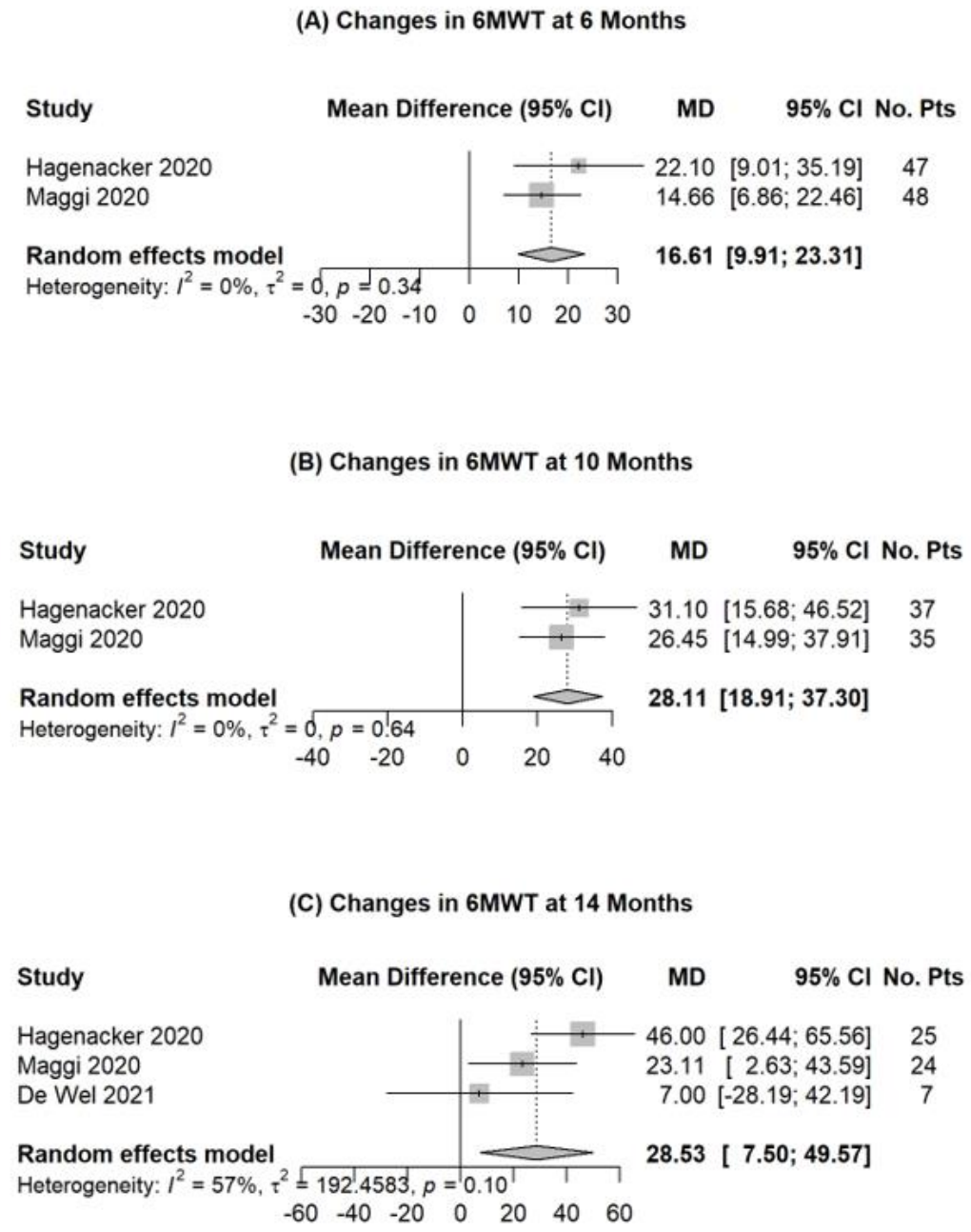


Source: Summary of clinical efficacy Figure 8 pg.67

6.46 As with the responder analysis for HFMSE, the method of estimating responders in Maggi 2020, which was the largest study in the meta-analysis for RULM responder, was likely misleading and overestimated the proportion of responders and therefore the results of the meta-analysis should be interpreted with caution.

6.47 The meta-analyses of the mean change in 6MWT distance are provided in Figure 5.

Figure 5: Mean Changes in 6MWT Distances (metres) From baseline to (A) 6 Months, (B) 10 Months, and (C) 14 Months After Nusinersen Initiation – Ambulatory Patients



Source: Summary of clinical efficacy Figure 11 pg.75

6.48 The average mean change in 6MWT failed to meet the criteria stated in the resubmission (≥30 metres change in 6MWT) to be considered clinically meaningful. The upper limit of the 95% confidence interval was greater than 30 metres at the 10 and 14 month time points, but not at the six month time point.

6.49 The percentage of patients with a clinically meaningful 6MWT response was only reported in the study by Maggi 2020, defined as at least a 30 metres change from baseline; hence a meta-analysis was not performed for this outcome. Maggi 2020 reported that 10/24 (42%) of patients treated with nusinersen achieved a clinically meaningful response in 6MWT at 14 months. When considering the total number of "walkers" initially treated in Maggi 2020, the proportion of patients who achieved a clinically meaningful response in 6MWT at 14 months was 10/48 (20.8%). As for responder analysis of HFMSE and RULM, the 6MWT responders at 14 months in Maggi 2020 should be interpreted with caution.

6.50 The PSCR provided a meta-analysis (Coratti 2021) that was published after the resubmission was lodged in November 2021. Coratti 2021 reported that amongst adult patients with SMA who were treated with nusinersen, longitudinal changes in motor function were consistently positive with the following improvements in pooled mean change observed: HFMSE 1.87 points (95% CI: 1.05-2.68), RULM 0.64 points (95% CI: 0.27-1.01), and 6MWT 20.28 metres (95% CI: 1.17-39.40). In addition to the studies identified in the resubmission, the meta-analysis by Coratti 2021 included additional studies Kessler 2020, Mendonca 2021, Osmanovic 2020, Konersman 2021 and Kizina 2020 that were not included in the resubmission. The meta-analysis also evaluated changes in untreated adults with SMA, finding consistently negative changes in HFMSE, RULM and 6MWT over a 10–14-month period.

6.51 Compared to the results reported in the resubmission for the meta-analysis of nusinersen studies from the EMA submission, the results reported by Coratti 2021 reported:

- similar mean changes in HFMSE at 14 months (resubmission: 1.86 points, 95% CI: 0.76 to 2.96, Figure 1, 7.08.COM.24);
- slightly lower changes in RULM at 14 months (resubmission: 1.05 points, 95% CI: 0.72 to 1.37, Figure 3, 7.08.COM.27); and
- slightly lower changes in 6MWT (resubmission: 28.53 metres, 95% CI: 7.50 to 49.5, Figure 5, 7.08.COM.29).

6.52 The results reported by Coratti 2021 also did not meet the proposed clinically meaningful difference for HFMSE (≥3 point change), RULM (≥2 point change) and 6MWT (improvement of ≥30 metres compared with baseline) proposed in the resubmission.

Comparative harms

6.53 No safety results were presented in the body of the resubmission. The EMA report detailed that cumulatively to 1 March 2021, of the total of 4544 events in the adult population that were reported in 2,417 cases, 538 events (12%) were serious and 4,006 events (88%) were non-serious. No comparative safety data was provided. Post lumbar puncture syndrome was the most common healthcare provider-confirmed event observed in adults receiving nusinersen. The most common consumer-reported adverse event occurring in adult patients was headache, followed by post lumbar puncture syndrome; however, headache is also associated with post lumbar puncture syndrome and may not be clearly differentiated in consumer-reported adverse events.

6.54 The updated Periodic Safety Update Report (PSUR) for nusinersen (31 May 2020 to 30 May 2021) was provided as an attachment to the resubmission. The PSUR (p 62) states "(t)he safety and efficacy of nusinersen in children aged newborn to 17 years has been established; however, there is limited exposure in patients over 18 years of age, and these data will continue to accrue as children age into adulthood. While there is no theoretical reason to suspect that patients over the age of 18 years will experience a differing safety profile to that observed in the indicated patient population, it is anticipated that adult patients with SMA may have more advanced disease and/or additional comorbidities not observed in paediatric patients, for which the impact on the safety of an individual patient receiving nusinersen is unknown."

6.55 As a claim of non-inferior safety was made by the resubmission, the lack of a comparative safety assessment was inappropriate. The PBAC had previously considered that the claim of non-inferior comparative safety was not adequately supported by the data and that there may be long term implications from repeated lumbar puncture administrations, particularly in patients who may not have had nusinersen otherwise (paragraphs 6.56 and 6.58, nusinersen PSD, November 2020 PBAC meeting).

Benefits/harms

6.56 As no comparative efficacy or safety data was presented in the resubmission, it did not allow for a quantitative comparison of the benefits and harms of treatment between nusinersen and standard of care in adult SMA patients. A benefits/harms table was consequently not presented.

Clinical claim

6.57 The resubmission described nusinersen for the treatment of adult patients diagnosed with SMA as having superior efficacy and non-inferior safety compared with standard of care.

6.58 As in previous resubmissions, the therapeutic conclusion was only partially supported by the evidence presented in the resubmission:

- In July 2021, the PBAC considered that the claim of superior comparative effectiveness was reasonable however, the PBAC considered that the magnitude and durability of benefit remained uncertain, noting no new comparative data was presented in the resubmission (paragraph 7.7, nusinersen PSD, July 2021 PBAC meeting). As there were no new randomised studies or other comparative evidence presented the incremental benefit of nusinersen in adult SMA patients remains uncertain.

- The PBAC had previously 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 (paragraph 7.8, nusinersen PSD, November 2020 PBAC meeting), with data up to 14 months of treatment being available. The additional studies included in this resubmission did not provide any longer term data to better inform the durability of benefit with nusinersen.

6.59 A claim of non-inferior safety remains unreasonable and was not adequately supported by the data. The PBAC had previously considered that the claim of non-inferior comparative safety was not adequately supported by the data and that there may be long term implications from repeated lumbar puncture administrations (paragraphs 6.56 and 6.58, nusinersen PSD, November 2020 PBAC meeting). The resubmission did not provide a comparative safety assessment to support a claim of non-inferiority, and only provided limited information regarding potential safety concerns with repeated lumbar punctures in the EMA report and the PSUR.

6.60 The PBAC considered that the claim of superior comparative effectiveness was reasonable, however the magnitude of benefit was difficult to quantify from the available evidence which was unchanged from the previous submission.

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

Economic analysis

6.62 The resubmission presented a cost-utility analysis that used the same economic model as presented in July 2021. The only changes made to the model were:

- a reduction in the price of nusinersen resulting in a proposed effective price of $/vial, representing a % reduction in the proposed price compared to the current effective price (an effective price of $/vial was proposed in the July 2021 resubmission); and

- a small change in the unit costs of nusinersen administration (from $ to $).

6.63 The only nusinersen study presented by the resubmission that was used to inform the economic evaluation was Maggi 2020. The resubmission stated that the new data

presented provides similar results in terms of response rates as used in the July 2021 economic model. However, the new data was not reported with the same level of granularity (response rates by instrument, SMA type, and ambulation status) as reported in Maggi 2020 and used in the economic model. Therefore, this new data was not incorporated into the economic model. The resubmission also did not use data from the natural history studies investigating adult patients with SMA to inform the economic evaluation, instead relying on Wadman 2017 in the economic model as with the July 2021 resubmission. Consequently, none of the new information from Elsheikh 2021a or the meta-analyses were used in the economic model.

6.64 As in the July 2021 resubmission, the resubmission proposed that the cost of [redacted] of the four loading doses of nusinersen will be rebated. The economic model therefore included only the cost of loading doses of nusinersen.

6.65 Table 10 provides a summary of the model structure and key inputs.

Table 10: Summary of model structure and rationale

Component	Summary
Time horizon	A lifetime time horizon was used in the model base case compared to 14 months follow up for Maggi 2020. The PBAC previously noted that while this time horizon was likely reasonable given the treatment and disease, the lifetime time horizon increased the uncertainty given the limited duration of available clinical data. (Table 15, p37, nusinersen PSD, November 2020 PBAC meeting).
Outcomes	QALYs
Methods used to generate results	Markov model
Treatments	Nusinersen and continuation of standard of care versus standard of care alone
Medical condition of the population	100% SMA patients Type III. This is in contrast to Maggi (SMA Type III 11% (other), Type III sitters (44%), Type III walkers (45%)) and Wadman 2017 (SMA Type I (26%), Type II (30%), Type III (41%), Type IV (3%)). The PBAC noted that while there may be some similarities between Type II and Type IIIa patients, there are numerous important differences such as life expectancy and degree of disability at any given age. As such, the progression and incremental benefit from treatment would differ (paragraph 6.63, nusinersen PSD, July 2021 PBAC meeting).
Health states	A total of nine unique health states: A separate health state was created for on or off nusinersen treatment for the below health states (except for the Dead health state) • Walking/standing: unaided – starting state assumed 34.3% of patients in this health state • Walking/standing: aided – starting state assumed 24.5 % of patients in this health state • Non-ambulatory: able to sit – starting state assumed 33.2% of patients in this health state • Non-ambulatory: unable to sit – starting state assumed 8% of patients in this health state • Dead – starting state assumed 0% of patients in this health state The proportion of patients starting in each health state was based on the proportion of Type III SMA patients in each ambulatory state from Wadman 2017.
Cycle length	1 year
Transition probabilities	The transition probabilities were dependent on age, SMA subtype and current health state, and treatment status. In the base case, a weighted proportion of each SMA subtype was assumed (50% Type IIIa, 35% Type IIIb with onset <12 years and 15% Type IIIb with onset >12 years) and this weighting was used to create one single survival curve for all patients to inform transition probabilities. The transition probabilities were calculated for each of the possible health state transitions in the model using the health state survival curves from Wadman 2017. The Markov model was structured such that patients can only move down through a single health state at a time.

<table>
<tr><th>Component</th><th>Summary</th></tr>
<tr><td></td><td>An annual discontinuation rate of 3.7% was applied in the model to account for nusinersen patients ceasing treatment. This figure is subject to considerable uncertainty and inconsistent with the discontinuation assumed in the financial estimates ([redacted]%).
Mortality was assumed to be the same for nusinersen and standard of care patients which was considered reasonable.
The model assumed that, while treated with nusinersen, patients would not decline into a less functional alive health state. This was previously considered unreasonable by ESC as data presented from Hagenacker 2020 and Walter 2019 indicated that some nusinersen treated patients experience a decline in motor function while receiving nusinersen treatment (Table 9, nusinersen PSD, November 2020 PBAC meeting).</td></tr>
<tr><td>Extrapolation method</td><td>The economic model extrapolated the survival curves from Wadman 2017 using the average annual probability of an event of the five years of the available data, resulting in zero or exceedingly small probabilities of progression through the health states after the end of the Wadman data (50 to 80 years depending on health state and type). This methodology was likely to be conservative but generally reflective of changes in the small patient numbers reported by Wadman 2017 and was unlikely to have substantial impact on the ICER. (Table 14, p33 nusinersen PSD, July 2021 PBAC meeting)</td></tr>
<tr><td>Utilities</td><td>Two types of utilities were included. Firstly, the utility of a particular health state was informed by Belter 2020, and secondly, patients treated with nusinersen were assumed to have a utility benefit from being on treatment which was informed by the responder rates obtained from Maggi 2020.
<table>
<tr><th rowspan="2">Health state</th><th colspan="3">Utility application in current resubmission</th></tr>
<tr><th>SOC</th><th>NUSI</th><th>Increment</th></tr>
<tr><td>Walking/standing: unaided</td><td>0.64</td><td>0.6817</td><td>0.0417</td></tr>
<tr><td>Walking/standing: aided</td><td>0.35</td><td>0.4214</td><td>0.0714</td></tr>
<tr><td>Non-ambulatory: able to sit</td><td>0.23</td><td>0.3014</td><td>0.0714</td></tr>
<tr><td>Non-ambulatory: unable to sit</td><td>0.14</td><td>0.2114</td><td>0.0714</td></tr>
</table>
SOC = standard of care, NUSI = nusinersen
Source: Table 3.20, p354 of the resubmission, table 9, p21-22 and paragraph 6.70, p25 nusinersen PSD November 2020 PBAC meeting.
The use of response rates from Maggi 2020 to inform utility benefits with nusinersen, as well as the derivation method led to a potential double counting of utility gains for the nusinersen treatment arm as some of the assumed utility gain from being a responder would have been captured by the individual health state utility. It was also noted that the utility benefit from nusinersen treatment accounted for 63% of the total incremental QALY gain with nusinersen in the base case of the economic model. (Table 15, p36 nusinersen PSD, July 2021 PBAC meeting)
There were no disutilities applied for adverse events in the model, though a disutility for adverse events associated with the lumbar puncture procedure may have been warranted. (Table 14, p33 nusinersen PSD, July 2021 PBAC meeting)</td></tr>
<tr><td>Disease state costs</td><td>Based on Klug 2016, as for previous resubmission. 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. (Table 14, p33 nusinersen PSD, July 2021 PBAC meeting)</td></tr>
<tr><td>Other nusinersen related costs</td><td>Costs for administration and adverse events were based on MBS item costs. As with the July 2021 resubmission, 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, which may not have been appropriate.</td></tr>
</table>

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

6.66 Key drivers of the model are presented in Table 11.

Table 11: Key drivers of the model

Description	Method/Value	Impact
Utility benefit from nusinersen treatment	In addition to utilities applied due to the health state of a given patient, a utility benefit was also applied for patients who were classified as being responders to nusinersen. This led to a potential double counting of utility gains for the nusinersen treatment arm as some of the assumed utility gain from being a responder would have been captured by the individual health state utility.	High, favours nusinersen. When the utility benefit attributed to nusinersen treatment was removed, the ICER increased by 169%.
Time horizon	A base case of a lifetime time horizon was used. While the time horizon was likely reasonable given the treatment and disease, the lifetime time horizon increased the uncertainty given the limited duration of available clinical data. Use of a 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.	High, favours nusinersen. When the time horizon was varied to 5, 10 and 20 years, the ICER increased by 71%, 50% and 23%, respectively
Responder rates from Maggi 2020	The responder rates from Maggi 2020 were used to define responders to nusinersen in the resubmission. The method of calculation likely biased the results in favour of nusinersen. An ITT approach may have been more appropriate.	High, favours nusinersen. When an ITT approach was used the ICER increased by 60%.
Assumption of nusinersen efficacy	In the base case, the relative risk of progression for nusinersen was assumed to be 0 (i.e. no progression). This was not supported by the clinical data.	Moderate, favours nusinersen. Assuming a relative risk of 0.5 increases ICER by 26%.

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

6.67 As noted in paragraph 6.62, only the price of nusinersen and cost of its administration was changed from the previous submission. All other efficacy and utility inputs, transition probabilities as well as model assumptions were unchanged. Given the lack of change in model structure and model inputs (except for the price of nusinersen and administration costs), the same observations and limitations noted for the model of the previous resubmission remain relevant. In its consideration of the July 2021 resubmission, the PBAC noted the following regarding the economic model:

- The only nusinersen study presented by the resubmission that was used to inform the economic evaluation, was Maggi 2020. There were significant issues with the application of responder rates from Maggi 2020 to estimate the utility benefits associated with nusinersen treatment (paragraph 6.71, nusinersen PSD, July 2021 PBAC meeting).

- The natural history studies used in the naïve comparison were not relied upon by the resubmission in the economic model. Instead, results from one natural history study, Wadman 2017, were used to inform the progression of disease in patients treated with standard of care (paragraph 6.61, nusinersen PSD, July 2021 PBAC meeting). Wadman 2017 was a study of 200 patients with genetically confirmed SMA Type I to IV, with SMN2 copy numbers varying from 1 to 5 copies. The age at symptom onset, motor milestones (sitting, standing, walking), respiratory support and other key events were reported for these patients, providing information on

the progression of disease in SMA patients. It was excluded from the clinical evidence as it did not report HFMSE, RULM or 6MWT results (though it is noted that results for some of these patients may have been reported by Wadman 2018) (paragraph 6.62, nusinersen PSD, July 2021 PBAC meeting).

- The resubmission excluded patients with SMA Type II from the economic analysis, arguing that Type II SMA made up only a small proportion of adult SMA patients in Maggi 2020 (13/116, 11%) and that Type IIIa patients were a suitable proxy for Type II patients. This may not be appropriate, particularly given that the requested restriction does not exclude patients with SMA Type II. The progression and incremental benefit from treatment would be likely to differ between Type II and Type IIIa patients. Further, both Hagenacker 2020 (45/124, 36%) and Duong 2021 (18/42, 42%) enrolled a much larger proportion of Type II patients compared to Maggi 2020. The omission of Type II SMA patients likely favoured nusinersen and underestimates the true ICER across the whole cohort as patients with Type II SMA were likely to start treatment at a more disabled health state, which may limit the potential utility gain from treatment with nusinersen.
- The ESC also recalled it had previously noted the economic model included a number of assumptions which were favourable to nusinersen, which remained relevant to the resubmission model, including:
  - Quality of life data being derived through two methods which are both subject to uncertainty, and likely to double count, to some extent, the effect of nusinersen. The ESC noted that quantification of QoL gains in the model was important because all benefit was based on utility gains (rather than mortality).
  - Assumption of no progression while treated with nusinersen, which was not supported by available evidence.
  - A lifetime time horizon with no decay of treatment effect despite study data being limited to around 14 months follow-up.

6.68 The PSCR (p3) asserted that by using a hierarchical approach to translating response to utility gains, the model likely underestimates rather than overestimates potential quality-of-life gains with nusinersen and that the model structure, based on gross motor function, implicitly underestimates the benefits in fine motor function associated with treatment.

6.69 While the current resubmission has proposed new continuation criteria, the resubmission (p67) stated that the July 2021 economic model had already applied a strictly enforced continuation rule and consequently no changes were required for the current model as a result of the changed continuation criteria proposed in the resubmission. The PSCR (p3) argued that this addresses the issue of the assumption of no progression while treated with nusinersen as patients with progression would

discontinue treatment. The rate applied was inconsistent with financial estimates an annual discontinuation rate of % was used (compared to 3.7% in the model).

6.70 Table 12 provides a summary of the results of the stepped economic evaluation presented in the resubmission.

Table 12: Stepped economic evaluation of nusinersen versus standard of care in adults with SMA

Treatment arm	Nusinersen	SoC	Difference
Step 1: Trial-based analysis, cost per patient responding to nusinersen on any measure of 6MWT, RULM or HFMSE			
Cost	$	$0	$
Responders	69%	0%	69%
Incremental cost per responder [a]			$
Step 2: Translate RULM response to utility gains [a]			
Cost	$	$0	$
QALYs	0.4298	0.3835	0.0463
Incremental cost per QALY			$ [1]
Step 3: Translate 6MWT response to utility gains (in ambulant patients only) [b]			
Cost	$	$0	$
QALYs	0.4367	0.3835	0.0532
Incremental cost per QALY			$ [d1]
Step 4: Translate remaining response to utility gains [c]			
Cost	$	$0	$
QALYs	0.4421	0.3835	0.0586
Incremental cost per QALY			$ [1]
Step 5: Extrapolate over patient lifetime			
Cost	$	$0	$
One point change in HFSME	7.0053	6.4349	0.5704
Incremental cost per one point change in HFSME			$
Step 6: Apply a reduction in the rate of progression through the health states applicable to nusinersen treatment			
Cost	$	$0	$
One point change in HFSME	7.5227	6.4349	1.0878
Incremental cost per one point change in HFSME			$
Step 7: Incorporate SMA related healthcare (health state) cost			
Cost	$	$186,283	$
QALYs	7.5227	6.4349	1.0878
Incremental cost per QALY			$ [1]

6MWT= six minute walking test; HFSME=Hammersmith Functional Motor Scale Extended; QALY=quality adjusted life year; RULM=revised upper limb module

[a] Proportion of patients treated with nusinersen who achieved ≥2 point change from baseline in RULM from Maggi 2020, assigned utility benefit of 0.120

[b] Proportion of ambulant patients treated with nusinersen who achieved >30 metre change from baseline on the 6MWT from Maggi 2020, but who were not already accounted for in step 2, assigned utility benefit of 0.050

[c] Proportion of patients treated with nusinersen who were classified as 'overall responders', defined as achieving at least one of: ≥3 point change from baseline on the HFMSE, ≥2 point change from baseline in RULM, or >30 metre change from baseline on the 6MWT, not previously accounted for in steps 2 or 3, assigned utility benefit of 0.030.

[d] Values reported in the PSCR could not be verified, value is based on the July 2021 resubmission.

Source: Table 3.43, p142 of the resubmission.

The redacted values correspond to the following ranges:

[1] > $1,055,000

6.71 The base case ICER was estimated by the model to be > $1,055,000 per QALY. Although the base case ICER was less than in previous resubmissions (compared to > $1,055,000 per QALY in July 2021 and > $1,055,000 per QALY in November 2020), it remains

considerably higher than the $355,000 to < $455,000/QALY previously accepted for the paediatric population.

6.72 For the model in the July 2021 resubmission, the PBAC considered that the level of confidence in the modelled benefits and the ICER was low, and the ICER was likely underestimated due to patients treated with nusinersen not being able to progress to lower health states while on treatment and a utility benefit being applied to both nusinersen treatment as well as response. The PBAC further noted the assumption of continued benefit for patients remaining on nusinersen over a lifetime time horizon was considerably uncertain given the available study data had only around 14 months follow-up (paragraph 7.8, nusinersen PSD, July 2021 PBAC meeting).

6.73 The PBAC previously considered that given the limited clinical data available for nusinersen in adult patients, any economic analysis for this patient population will be associated with substantial uncertainty. As such, the PBAC advised that a substantial price reduction in combination with a MAP would be required to address the uncertainty around the magnitude and duration of clinical benefit associated with nusinersen treatment and achieve a cost-effective listing in adult patients. The PBAC considered that the price reduction should reflect the benefit of treatment in adult patients relative to that for paediatric patients (paragraph 7.10, nusinersen PSD, July 2021 PBAC meeting).

6.74 The results of the univariate sensitivity analyses conducted by the resubmission and during the evaluation of the economic model are shown in Table 13.

Table 13: Results of sensitivity analyses

Scenario	Incremental costs	Incremental QALYs	ICER	Change from base case
Base case	**$**	**1.0878**	**$** [4]	**-**
Time horizon, years (base case: lifetime)				
5	$	0.2562	$ [4]	+71%
10	$	0.4537	$ [4]	+50%
20	$	0.7555	$ [4]	+23%
30	$	0.9397	$ [4]	+10%
Progression relative ratio, nusinersen versus SoC (base case: RR=0, i.e., no progression on treatment)				
RR=0.1	$	1.0203	$ [4]	+5%
RR=0.25	$	0.9273	$ [4]	+12%
RR=0.5	$	0.7908	$ [4]	+26%
RR=1.0	$	0.5704	$ [4]	+64%
Annual discontinuation rate (base case: 3.7%)				
0%	$	1.7542	$ [4]	-2%
5%	$	0.9420	$ [4]	+2%
7.5% [a]	$	0.7337	$ [4]	+6%
10%	$	0.5886	$ [4]	+11%
Health state utilities (base case: Belter 2020)				
Lloyd 2019	$	1.6144	$ [3]	-33%
Treatment utility benefit (base case: walkers=0.0417, others=0.0714)				
Walkers=0.0834, others=0.1428	$	1.7711	$ [2]	-39%
Walkers=0.0209, others=0.0357	$	0.7464	$ [4]	+46%
Zero	$	0.4045	$ [4]	+169%
Walkers = 0.0417, others = 0.0426[b]	$	0.8767	$ [4]	+24%
Health state costs [4]				
Zero	$	1.0878	$ [4]	+1%
Decrease 50%	$	1.0878	$ [4]	+0.5%
Increase 50%	$	1.0878	$ [4]	-0.5%
Increased 300%	$	1.0878	$ [4]	-2%
Discount rate (base case: 5%)				
0%	$	2.8556	$ [4]	-29%
3.5%	$	1.3807	$ [4]	-8%
Response rates for HSFME, RULM and 6MWT (base case: percentages as reported by Maggi 2020)				
Responder rates using figures from Maggi 2020 using total number of patients (ITT) as denominator	$	0.6792	$ [4]	+60%
Price reduction required to achieve ICER $ [1]/QALY, as for paediatric Type II/IIIa (base case nusinersen per dose $)				
ICER $ [1]/QALY (same as paediatric Type II/IIIa) – Cost per nusinersen dose $	$	1.0878	$ [1]	-77%

6MWT = six minute walk test HFMSE = Hammersmith Functional Motor Scale-Expanded; ICER=incremental cost-effectiveness ratio; ITT = intention to treat; QALYs=quality adjusted life years; RR=relative risk, RULM = revised upper limb module

Values in italics were additional analyses conducted during the evaluation.

[a] annual discontinuation rate used in Section 4 of the resubmission

[b] estimated by calculating responder from HFMSE (58%) first, then assuming remaining 21% of responders were RULM responders rather than the reverse.

Source: Table 3.53, p151 of the resubmission

The redacted values correspond to the following ranges:

[1]$355,000 to < $455,000

[2]$855,000 to < $955,000

[3]$955,000 to < $1,055,000

[4]> $1,055,000

6.75 As in previous resubmissions, the biggest driver in the model is the cost of nusinersen because the gain in QALYs is relatively small. A scenario in which the price of nusinersen was reduced to $ (a further % reduction from the proposed price of $) brought the ICER down to $355,000 to < $455,000 /QALY, which was consistent with the ICER accepted by the PBAC for the treatment of paediatric patients with Type II and IIIa SMA with nusinersen (Table 6, p18 nusinersen PSD, March 2018 PBAC meeting).

6.76 The pre-PBAC proposed a further reduction in the price of nusinersen to $ per vial, a % decrease compared with the effective price in the paediatric setting. This reduced the ICER to $855,000 to < $955,000/QALY.

Drug cost/patient/year

6.77 The drug cost per patient for the first year of treatment, including four loading doses (of which was rebated by the sponsor) and two maintenance doses, was $ This was reduced to $ at $ per vial as proposed in the pre-PBAC response. The cost per year for nusinersen maintenance was $, based on three maintenance doses per year (reduced to $ at $ per vial). The rebate for of the four loading doses was accounted for in both the economic evaluation and the financial estimates.

Table 14: Drug cost per patient for proposed drug

	Study dose and duration	Economic Model	Financial estimates
Mean dose	12 mg	12 mg	12 mg
Mean duration	~14 months	Lifetime	Lifetime
Cost/patient/dose	$	$	$
Pre-PBAC cost/patient/dose	$	$	$

Estimated PBS usage & financial implications

6.78 This resubmission was not considered by DUSC. 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 2020, November 2017 and July 2021 PBAC (re)submissions for nusinersen.

6.79 The estimated financial impact of listing nusinersen on the PBS for the treatment of adult SMA patients with symptom onset before 19 years of age is summarised in Table 15.

Table 15: Estimated net financial implications of the proposed nusinersen listing

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimation of use and financial impact of the proposed medicine (PBS and RPBS)						
Prevalent patient population						
Type I	[redacted][1]					
Type II	[redacted][1]					
Type III	[redacted][1]					
Total	[redacted][1]					
Initiators per year [a]						
Type II	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Type III	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Total	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Total patients [a]						
Type II	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Type III	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Total	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Vials/administrations of nusinersen (excluding [redacted] free initiation dose received) [a]						
Total	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Revised in pre-PBAC response to account for [redacted] grandfather patients	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Vials/administrations of nusinersen (all doses, including [redacted] free initiation dose received) [a]						
Total	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Estimated financial implications for the PBS/RPBS						
Type II	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]
Type III	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]
Net cost to PBS/RPBS	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]
Net cost to PBS/RPBS (revised pre-PBAC price)	$[redacted][2]	$[redacted][2]	$[redacted][3]	$[redacted][2]	$[redacted][2]	$[redacted][2]
Estimation of changes in use and financial impact of other medicines (PBS and RPBS)						
The resubmission appropriately assumed no therapies were expected to be substituted.						
Estimated financial implications for the health budget						
MBS administration costs						
MBS administration costs	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]
Adverse events costs						
Adverse Event costs	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]
Net cost to Government health budget						
Total	**$[redacted][3]**	**$[redacted][3]**	**$[redacted][3]**	**$[redacted][3]**	**$[redacted][3]**	**$[redacted][3]**
Total (revised pre-PBAC price)	**$[redacted][2]**	**$[redacted][2]**	**$[redacted]**	**$[redacted][2]**	**$[redacted][2]**	**$[redacted][2]**

eff = effective; pub = published

[a]Figures rounded to the nearest whole number. Total figures for Type II + Type III may not add up due to rounding.

Source: Table 4.3, 4.4, 4.6, p158, 159, 160, 161 of the resubmission, sheet '3a. Scripts – proposed' and '3b. Impact – proposed (pub)' of the financial model workbook, and Table 4.2.1, p138 of the July 2021 commentary.

The redacted values correspond to the following ranges:

[1]*< 500*

[2]*$0 to < $10 million*

[3]*$10 million to < $20 million*

6.80 The predicted use of the nusinersen for the treatment of adults with SMA was calculated in the same way as in the previous July 2021 resubmission except for the following changes:

- Different rates of nusinersen uptake were used. The resubmission used uptake rates of % in Year 1 increasing to % in Year 6 (compared to % in Year 1 and % in Year 6 in the previous resubmission); and
- A discontinuation rate of % per year was used (compared to 3.7% per year in the previous resubmission). This was inconsistent with the economic model in the current resubmission where a discontinuation rate of 3.7% used. The PBAC noted that this may underestimate the utilisation of nusinersen, however any underestimation would be conservative in the context of an RSA with a % rebate over the caps.

6.81 In the resubmission the estimated net cost to the government budget of listing nusinersen on the PBS/RPBS for adult SMA patients with symptom onset before 19 years of age at the proposed effective price was $10 million to < $20 million in Year 1, decreasing slightly to $10 million to < $20 million in Year 6. The total cost over the six year forward estimates was $100 million to < $200 million. With the revised pre-PBAC response price, and including the < 500 patients who have already commenced treatment on the sponsor's access program the net cost for nusinersen decreased to $0 to < $10 million in Year 1, increasing to $0 to < $10 million in Year 6. The total cost over the six year forward estimates was $50 million to < $60 million.

6.82 The estimated prevalent population remained unchanged from the estimates used in the November 2020 and November 2017 submission. The PBAC previously concluded that the prevalent population with SMA Types I to III was likely to have been underestimated, particularly for the number of patients over the age of 18 years. The evaluation considered that uptake rates of % in Year 1, increasing by % per year so that % of the total prevalent pool would be on treatment with nusinersen by Year 6 of listing, may have been underestimated considering there were no other disease modifying drugs for SMA PBS listed for the proposed population. The ESC noted that uptake rates in the nusinersen access program may help inform likely uptake rates, though uptake would also be impacted by access programs for risdiplam. The pre-PBAC response (p3) noted that the uptake is expected to be limited and tempered by patient choice, suitability of spinal access for intrathecal administration and the overall risk-benefit assessment between patient and clinician. The Pre-PBAC response also stated that a modest uptake rate has been observed in the nusinersen access program. In the months since the access program commenced there are < 500 patients (% from total estimated population of < 500) enrolled. The PBAC noted that this was also consistent with clinical input from the sponsor hearing and considered that the uptake rates appeared to be reasonable.

6.83 The PBAC also noted that the eligible adult SMA population is limited and will diminish over time as all children with SMA will have been offered nusinersen or other disease modifying treatment on the PBS.

Financial Management – Risk Sharing Arrangements

6.84 The resubmission proposed an RSA to manage the uncertainty regarding the number of adults treated with nusinersen and the financial estimates. The resubmission proposed an expenditure cap specifically for utilisation of nusinersen in adults with a rebate to be applied on any additional PBS expenditure over the subsidisation caps.

6.85 The proposed subsidisation cap figures, based on the revised pre-PBAC price are detailed in Table 16. These values were equal to the expected nusinersen PBS expenditure estimates, excluding rebates for [redacted] (as shown in Table 15).

Table 16: Proposed subsidisation caps for the RSA

Total cost of nusinersen to PBS	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Pre-PBAC revised caps (vial price $[redacted])	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]

Source: Table 5.1, p164 of the resubmission

6.86 The resubmission stated that the exact rebate above the subsidisation caps will be confirmed following a PBAC recommendation.

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

7 PBAC Outcome

7.1 The PBAC recommended the listing of nusinersen for the treatment of adult patients (older than 18 years of age) diagnosed with spinal muscular atrophy (SMA) with symptom onset before 19 years of age (primarily SMA Types II and III), on the basis that it should be available only under special arrangements under Section 100. The PBAC is satisfied that nusinersen provides, for some patients, a significant improvement in efficacy over standard care. The PBAC recognised the clinical need for effective treatments for adults with SMA. The PBAC noted that the changes to the restrictions proposed in the resubmission were based on consultation with patients and clinicians and considered this helped to ensure the adult population most likely to benefit from treatment was sufficiently defined. The PBAC also noted that the sponsor proposed a substantial price reduction in the pre-PBAC response to better reflect the benefit of treatment in adult SMA patients. The sponsor also proposed a risk sharing arrangement which accounts for the number of patients treated and the number of patients who respond to treatment. The PBAC considered that a review of uptake and continuation rates in adult SMA patients should take place within three years after listing.

7.2 The PBAC acknowledged there was a high clinical need for treatments to be made available to adult SMA patients and equity of access to treatment across ages was an important consideration. The PBAC noted the condition is substantially debilitating and there are no PBS subsidised therapies available. The PBAC noted that patients

reported fear and grief associated with functional decline over time and particularly for the loss of independence. The PBAC noted the consumer comments indicated that slowing disease progression and even small improvements in functioning were highly valued by adult SMA patients as these outcomes may allow patients to continue employment and maintain independence.

7.3 The PBAC noted that extensive consultation between clinicians and adults with SMA was valuable in informing the restrictions to ensure the adult population most likely to benefit from treatment was sufficiently defined. The PBAC noted that the resubmission proposed a continuation rule to assess response to treatment, such that only patients benefiting from nusinersen would receive ongoing treatment. The PBAC noted that the resubmission proposed that restrictions state that treatment must be ceased when there is evidence of a clinically significant decline in motor function due to disease progression, as assessed on two consecutive occasions (4-6 months apart) (compared to baseline). A clinically significant decline was defined as a decrease in a motor function outcome (RULM, HFMSE, or 6MWT); and a decrease in a patient reported outcome (spinal muscular atrophy health index (SMA-HI) or spinal muscular atrophy function rating scale (SMAFRS)). The PBAC noted that subsequent consultation between clinicians and adults with SMA suggested that patient reported outcome measures (such as SMA-HI and SMAFRS) are likely to be useful tools in guiding consultation with the neuromuscular specialist but that they would not be suitable for inclusion in the restriction as a basis for continuation/discontinuation. The PBAC also noted that patients recognised the need for discontinuation of treatment where a sustained decline in function is evident. The recommendation from consultation with adults living with SMA was that treatment effectiveness should be determined using information from a combination of validated physical assessments, patient reported outcome measures and consultation between the adult living with SMA and the neuromuscular specialist. The PBAC considered that it would be appropriate to amend the proposed restrictions for the continuing listing to reflect this recommendation, rather than sole reliance on functional outcomes (RULM, HFMSE, 6MWT) and patient reported outcomes (SMA-HI, SMAFRS).

7.4 The PBAC noted that the resubmission proposed that treatment should continue for at least 15 months before being assessed (based on consultation with an advisory board of 4 clinicians). The PBAC noted that subsequent consultation between clinicians and adults with SMA suggested that a timeframe of 2 years would be appropriate for assessment of treatment response. The PBAC considered the restrictions should require that assessment of suitability for continuation of treatment takes place every 6 months after 2 years of treatment.

7.5 The PBAC noted that the clinical place and comparator for nusinersen were unchanged from previous submissions and considered that they remain appropriate as there are no other disease-modifying treatments for SMA in adult patients currently PBS listed. The PBAC welcomed the advice in the pre-PBAC response that the sponsor is willing to progress the PBS listing for Type IIIb patients following a positive recommendation

for the adult population.

7.6 The PBAC noted that the evidence base remained almost unchanged from the previous resubmission. As in previous (re)submissions, no randomised trials or other comparative efficacy evidence was identified, and no studies with longer term follow-up beyond 14 months were available.

7.7 The PBAC previously considered that while a claim of superior comparative effectiveness of nusinersen to standard of care was reasonable, the magnitude and durability of benefit was not able to be quantified based on the data presented (paragraph 6.32, nusinersen PSD, July 2021 PBAC meeting). The PBAC maintained that although there was clear benefit for adult SMA patients, which was supported by real world experience with nusinersen, the magnitude of benefit remained difficult to quantify and the durability of treatment benefit remained uncertain.

7.8 The PBAC previously considered that the claim of non-inferior comparative safety was not adequately supported by the data and that there may be long term implications from repeated lumbar puncture administrations (paragraph 7.7, nusinersen PSD, July 2021 PBAC meeting). The PBAC considered this was unchanged from the resubmission and that uptake of nusinersen in the adult population may be somewhat limited by safety considerations.

7.9 The PBAC noted that the same economic model and cost-utility analysis as presented in the July 2021 resubmission was presented in the current resubmission, with the only changes made being a reduction in the price of nusinersen and a small change in the unit costs of nusinersen administration. The PBAC recalled it previously considered that "the level of confidence in the modelled benefits and the ICER was low, and the ICER was likely underestimated due to patients treated with nusinersen not being able to progress to lower health states while on treatment and a utility benefit being applied to both nusinersen treatment as well as response. The PBAC further noted the assumption of continued benefit for patients remaining on nusinersen over a lifetime time horizon was considerably uncertain given the available study data had only around 14 months follow-up" (paragraph 7.8, nusinersen PSD, July 2021 PBAC meeting). The PBAC considered that a high level of uncertainty regarding the modelled benefits and ICER remained, as the model structure and inputs were largely unchanged from the July 2021 resubmission. However, the PBAC acknowledged the uncertainty reflected the evidence available. The PBAC noted that the ICER in the resubmission (> $1,055,000 /QALY) remained very high even with the [redacted]% price reduction compared with the July 2021 resubmission.

7.10 The PBAC recalled it previously advised that "a substantial price reduction commensurate with the benefit of treatment in adult SMA patients… would be required to achieve a cost-effective listing for adult SMA patients" (para 7.1 nusinersen PSD, July 2021 PBAC Meeting). The sponsor's pre-PBAC response proposed a reduced price of $[redacted] per vial, with [redacted] loading dose, reducing the ICER to $855,000 to < $955,000/QALY. The PBAC considered that the ICER remained high, but

that the revised price represented a substantial reduction compared with the price in the paediatric population and better reflected the benefit of treatment in adult SMA patients. The PBAC considered that at the revised price the cost-effectiveness of nusinersen was acceptable in the context of very high clinical need in a limited and diminishing population and where equity of access is an additional consideration.

7.11 The PBAC noted that the same approach was used for the financial estimates as in the July 2021 resubmission, with changes to the effective price and the increased discontinuation rate (%) consistent with the restriction requirements for ongoing assessment of response for continuing treatment. The PBAC recalled it previously considered the financial estimates were uncertain and associated with a low level of confidence (paragraph 7.13, nusinersen PSD, July 2021 PBAC meeting). The PBAC noted that the pre-PBAC response (p3) stated that the uptake is expected to be limited and tempered by patient choice, suitability of spinal access for intrathecal administration and the overall risk-benefit assessment between patient and clinician. The PBAC noted that this was consistent with the modest uptake in the nusinersen access program and with clinical input from the sponsor hearing.

7.12 The PBAC considered that given the remaining uncertainty regarding potential uptake and continuation rates in adult SMA patients, a review should take place within three years after listing. The PBAC noted that the sponsor would need to provide relevant data from the SMA registry to inform the review of uptake and continuation rates. The PBAC considered that review of the rates of treatment continuation may also be informative in assessing the ongoing effectiveness of nusinersen in the adult population as perceived by patients and clinicians.

7.13 The PBAC noted that the reduced requested vial price for nusinersen considerably reduced the overall financial impact of listing and the requested caps for the proposed RSA. The PBAC considered that this provided assurance that the additional financial impact for expanding access to the adult population was limited and commensurate with the benefit expected in adult patients. In addition to the proposed rebate for loading dose, the PBAC considered that a % rebate for use above the financial caps from the pre-PBAC response (see Table 16) would be appropriate given the high cost of treatment and the residual uncertainty regarding the cost-effectiveness of treatment in the adult SMA population and the potential for ongoing treatment in patients for whom there is little or no benefit from treatment.

7.14 The PBAC noted that a flow-on change to the existing continuing listings for nusinersen and risdiplam would be required to ensure that patients initiated on treatment as adults can only receive continuing treatment under the listing specific to adult SMA patients (where assessment of continuing benefit is required for ongoing treatment).

7.15 The PBAC found that the criteria prescribed by the National Health (Pharmaceuticals *and Vaccines – Cost Recovery) Regulations 2009* for Pricing Pathway A were not met. Specifically the PBAC found that in the circumstances of its recommendation for nusinersen:

a) The treatment may not provide a substantial and clinically relevant improvement in efficacy over alternative therapies given the uncertainty in the magnitude of benefit in the adult population;

b) The treatment is expected to address a high and urgent unmet clinical need;

c) It was not necessary to make a finding in relation to whether it would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A because one or more of the preceding tests had failed.

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

7.17 The PBAC noted that additional changes to the restrictions may be required before listing can proceed.

Outcome:
Recommended

8 Recommended listing

Amend existing listing as follows:

MEDICINAL PRODUCT medicinal product pack	**PBS item code**	**Max. qty packs**	**Max. qty units**	**№.of Rpts**	**Available brands**
NUSINERSEN					
nusinersen 12mg/5 mL injection, 5 mL vial	New (Pub) New (Priv)	1	1	3	Spinraza
		Max.qty (packs) multiplier = 1 Repeat increases: nil			
Add new Restriction Summary [new] / Treatment of Concept: [new]					
	Category / Program: Section 100 – Highly Specialised Drugs Program (Public/Private hospitals)				
	Prescriber type: ☒ Medical Practitioners				
	Restriction type: ☒Authority Required – non-immediate assessment by Services Australia				
Prescribing rule level	**Administrative Advice:** No increase in the maximum quantity or number of units may be authorised.				
	Administrative Advice: No increase in the maximum number of repeats may be authorised.				
	Administrative Advice: Special Pricing Arrangements apply.				
	Indication: Spinal muscular atrophy (SMA)				
	Treatment Phase: Initial treatment of symptomatic SMA - Loading doses				
	Treatment criteria:				
New					
	AND				
	Clinical criteria:				
	The condition must have genetic confirmation of 5q homozygous deletion of the survival motor neuron 1 (SMN1) gene; or				

	The condition must have genetic confirmation of deletion of one copy of the SMN1 gene in addition to a pathogenic/likely pathogenic variant in the remaining single copy of the SMN1 gene
	AND
	Clinical criteria:
	Patient must have experienced at least two of the defined signs and symptoms of SMA prior to 19 years of age
	AND
	Clinical criteria:
	The treatment must not be used in combination with other SMA disease-modifying treatments, including risdiplam, for this condition;
	Clinical criteria:
	AND
	The patient must not be receiving invasive permanent assisted ventilation in the absence of a potentially reversible cause while being treated with this drug.
	AND
	Clinical criteria:
	The treatment must be given concomitantly with best supportive care for this condition
	AND
	Clinical criteria:
	The treatment must not exceed four loading doses (at days 0, 14, 28 and 63) under this restriction
	AND
	Population criteria:
	Patient must be 19 years of age or older
	Prescribing Instructions: Defined signs and symptoms of SMA are: i) Onset before 19 years of age; and ii) Failure to meet or regression in ability to perform age-appropriate motor milestones; or iii) Proximal weakness; or iv) Hypotonia; or v) Absence of deep tendon reflexes; or vi) Failure to gain weight appropriate for age; or vii) Any active chronic neurogenic changes; or viii) A compound muscle action potential below normative values for an age-matched child.
	Prescribing Instructions: Application for authorisation of initial treatment must be in writing and must include: (a) a completed authority prescription form; and (b) a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice) which includes the following: (i) specification of SMA type; and (ii) sign(s) and symptom(s) that the patient has experienced; and (iii) patient's age at the onset of sign(s) and symptom(s).
	Administrative Advice: An outcome on the authority application is not immediate, but will follow in due course. Electronic upload is encouraged to reduce processing time.
	Administrative Advice: Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos

	Or mailed to: Services Australia Complex Drugs Reply Paid 9826 HOBART TAS 7001

MEDICINAL PRODUCT **medicinal product pack**	**PBS item code**	**Max. qty packs**	**Max. qty units**	**№.of Rpts**	**Available brands**
NUSINERSEN					
nusinersen 12mg/5 mL injection, 5 mL vial	New (Pub) New (Priv)	1	1	0	Spinraza
		Max.qty (packs) multiplier = 1 Repeat increases: nil			

Add new Restriction Summary [new] / Treatment of Concept: [new]	
	Category / Program: Section 100 – Highly Specialised Drugs Program (Public/Private hospitals)
	Prescriber type: ☒ Medical Practitioners
	Restriction type: ☒ Authority Required – immediate/real-time assessment by Services Australia
Prescribing rule	**Administrative Advice:** No increase in the maximum quantity or number of units may be authorised.
Prescribing rule	**Administrative Advice:** No increase in the maximum number of repeats may be authorised.
Prescribing rule	**Administrative Advice:** Special Pricing Arrangements apply.
	Indication: Spinal muscular atrophy (SMA)
	Treatment Phase: Continuing/maintenance treatment of symptomatic spinal muscular atrophy (SMA)
	Treatment criteria:
	Must be treated by a specialist medical practitioner experienced in the diagnosis and management of SMA; or in consultation with a specialist medical practitioner experienced in the diagnosis and management of SMA.
	Clinical criteria:
	Patient must have previously initiated PBS-subsidised treatment with this drug for this condition at the age of 19 years or older
	AND
	Clinical criteria:
	The treatment must not be used in combination with other SMA disease-modifying treatments, including risdiplam, for this condition;
	AND
	Clinical criteria:
	The treatment must be given concomitantly with best supportive care for this condition
	AND
	Clinical criteria: 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
	Clinical criteria:
	Patient must demonstrate a clinically meaningful response to treatment, following 2 years of treatment
	Prescribing Instructions: Prior to continuing treatment, a comprehensive assessment must be undertaken and documented, involving the patient and the treating physician to establish agreement that treatment is continuing to produce worthwhile benefit. Treatment should cease if there is no agreement of benefit.

	Re-assessments for a clinically meaningful response are to be undertaken and documented every six months. Clinically meaningful response to treatment is defined as improvement, stabilisation or minimal decline in symptoms as demonstrated in the following areas: Maintenance of motor function as assessed using Revised Upper Limb Module (RULM), Hammersmith Functional Motor Scale – Expanded (HFMSE) and/or 6-minute walk test (6MWT). Maintenance of patient's quality of life including but not limited to level of independence. This may be informed by completion of the patient reported outcome measures SMA health index (SMA-HI) or SMA functional rating scale (SMAFRS).
	Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).

MEDICINAL PRODUCT **medicinal product pack**	**PBS item code**	**Max. qty packs**	**Max. qty units**	**№.of Rpts**	**Available brands**
NUSINERSEN					
nusinersen 12mg/5 mL injection, 5 mL vial	New (Pub) New (Priv)	1	1	0	Spinraza
		Max.qty (packs) multiplier = 1 Repeat increases: nil			

Add new Restriction Summary [new] / Treatment of Concept: [new]		
		Category / Program: Section 100 – Highly Specialised Drugs Program (Public/Private hospitals)
		Prescriber type: ☒ Medical Practitioners
		Restriction type: ☒Authority Required – non-immediate assessment by Services Australia
Prescribing rule level		**Administrative Advice:** No increase in the maximum quantity or number of units may be authorised.
		Administrative Advice: No increase in the maximum number of repeats may be authorised.
		Administrative Advice: Special Pricing Arrangements apply.
		Indication: Spinal muscular atrophy (SMA)
		Treatment Phase: Transitioning from non-PBS to PBS subsided treatment – 'Grandfather' treatment
		Clinical criteria:
		Patient must have received non-PBS subsidised treatment with this drug for this PBS indication prior to [date of listing]
		Treatment criteria:
		Must be treated by a specialist medical practitioner experienced in the diagnosis and management of SMA; or in consultation with a specialist medical practitioner experienced in the diagnosis and management of SMA.
		AND
		Clinical criteria:
		The condition must have genetic confirmation of 5q homozygous deletion of the survival motor neuron 1 (SMN1) gene; or The condition must have genetic confirmation of deletion of one copy of the SMN1 gene in addition to a pathogenic/likely pathogenic variant in the remaining single copy of the SMN1 gene
		AND
		Clinical criteria:
		Patient must have experienced at least two of the defined signs and symptoms of SMA prior to 19 years of age
		AND

	Clinical criteria:
	The treatment must not be used in combination with other SMA disease-modifying treatments, including risdiplam, for this condition;
	Clinical criteria:
	AND
	The patient must not be receiving invasive permanent assisted ventilation in the absence of a potentially reversible cause while being treated with this drug.
	AND
	Clinical criteria:
	The treatment must be given concomitantly with best supportive care for this condition
	AND
	Population criteria:
	Patient must be 19 years of age or older at the time of initial treatment with this drug.
	Prescribing Instructions: Defined signs and symptoms of SMA are: i) Onset before 19 years of age; and ii) Failure to meet or regression in ability to perform age-appropriate motor milestones; or iii) Proximal weakness; or iv) Hypotonia; or v) Absence of deep tendon reflexes; or vi) Failure to gain weight appropriate for age; or vii) Any active chronic neurogenic changes; or viii) A compound muscle action potential below normative values for an age-matched child.
	Prescribing Instructions: Application for authorisation of initial treatment must be in writing and must include: (a) a completed authority prescription form; and (b a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice) which includes the following: (i) specification of SMA type; and (ii) sign(s) and symptom(s) that the patient has experienced; and (iii) patient's age at the onset of sign(s) and symptom(s).
	Prescribing instructions: A patient may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a Grandfathered patient must qualify under the Continuing treatment criteria.
	Administrative Advice: An outcome on the authority application is not immediate, but will follow in due course. Electronic upload is encouraged to reduce processing time.
	Administrative Advice: This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria.
	Administrative Advice: Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos Or mailed to: Services Australia Complex Drugs Reply Paid 9826 HOBART TAS 7001

Flow on changes to nusinersen (11378W, 11476B) and risdiplam (12606L, 12609P) continuing restrictions - add population criteria:

	Population criteria:
	Patient must have been 18 years of age or younger at the time of initial treatment with this drug.

*These restrictions may be subject to further review. Should there be any changes made to the restriction the Sponsor will be informed**.***

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

10 Sponsor's Comment

Biogen welcomes the PBAC's decision to recommend nusinersen for adults diagnosed with SMA with symptom onset before 19 years of age. Biogen would like to take this opportunity to thank the SMA community and healthcare professionals who supported the submission. Biogen looks forward to working with the Department of Health to secure a PBS listing for nusinersen in adults with SMA at the earliest possible opportunity.