Record of the Rare Disorders Subcommittee meeting held at PHARMAC on 24 September 2019 (record for web publishing)

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Note that this document is not necessarily a complete record of the Rare Disorders Subcommittee meeting; only the relevant portions of the record relating to Rare Disorders Subcommittee discussions about an application or PHARMAC staff proposal that contains a recommendation are generally published.

The Rare Disorders Subcommittee may:

a) recommend that a pharmaceutical be listed by PHARMAC on the Pharmaceutical Schedule and the priority it gives to such a listing;

b) defer a final recommendation, and give reasons for the deferral (such as the supply of further information) and what is required before further review; or

c) recommend that PHARMAC decline to list a pharmaceutical on the Pharmaceutical Schedule.

These Subcommittee minutes will be reviewed by PTAC at its February 2020 meeting.

1. Nusinersen for the treatment of spinal muscular atrophy (SMA) - resubmission

Application

1.1. The Subcommittee reviewed a resubmission from Biogen Australia Pty Ltd for nusinersen (Spinraza) for the treatment of spinal muscular atrophy that included revised eligibility criteria and updated clinical trial data.

1.2. The Subcommittee took into account, where applicable, PHARMAC's relevant decision-making framework when considering this agenda item.

Recommendation

1.3. The Subcommittee **recommended** nusinersen be funded with a **high** priority, within the context of the rare disorders therapeutic area, for the treatment of pre-symptomatic individuals with spinal muscular atrophy and two or three *SMN2* copies, subject to the Special Authority criteria below. This recommendation was based on the absence of funded alternatives, the high health need of these individuals and their family/whānau, longer-term evidence of survival gain and meaningful clinical benefit with nusinersen, and that patients with pre-symptomatic SMA had the greatest potential to benefit.

Initiation – spinal muscular atrophy (SMA) – pre-symptomatic

Applications only from, or in consultation with, a specialist medical practitioner experienced in the diagnosis and management of SMA associated with a neuromuscular clinic of a recognised hospital in the management of SMA.

Re-assessment required after 12 months

All of the following:

1. Genetic documentation of 5q SMA homozygous gene deletion, homozygous mutation, or compound heterozygous mutation, identified via newborn screening; and
2. Patient must be pre-symptomatic; and
3. Patient must have only two or three copies of *SMN2*; and
4. Treatment must be given concomitantly with standard of care for this condition; and
5. Treatment must not exceed four loading doses (at days 0, 14, 28 and 63); and
6. Patient must be 18 years of age or under.

Continuation – spinal muscular atrophy (SMA) – pre-symptomatic
Applications only from, or in consultation with, a specialist medical practitioner experienced in the diagnosis and management of SMA associated with a neuromuscular clinic of a recognised hospital in the management of SMA.
Re-assessment required after 12 months
All of the following:

1. Patient must have had a previous approval for nusinersen; and
2. Treatment must be given concomitantly with standard of care for this condition; and
3. There has been demonstrated maintenance of motor milestone function (as assessed using age-appropriate scales: the HINE Section 2, CHOP INTEND, or HFMSE) since treatment initiation; and
4. The patient does not require invasive permanent assisted ventilation (see Note).

Note:
Invasive permanent assisted ventilation means:
Ventilation via tracheostomy tube for greater than or equal to 16 hours per day.

1.4. The Subcommittee **recommended** nusinersen be funded with a **medium** priority, within the context of the rare disorders therapeutic area, for the treatment of symptomatic patients with type I, II, and IIIa spinal muscular atrophy, subject to the Special Authority criteria below. This recommendation was based on the absence of funded alternatives, the high health need of these individuals and their family/whānau, evidence of survival gain for infantile onset SMA and meaningful clinical benefit for all symptomatic subgroups considered.

Initiation – spinal muscular atrophy (SMA) – symptomatic type I, II and IIIa

Applications only from or in consultation with a specialist medical practitioner experienced in the diagnosis and management of SMA associated with a neuromuscular clinic of a recognised hospital in the management of SMA.

Re-assessment required after 12 months
All of the following:

1. Genetic documentation of 5q SMA homozygous gene deletion, homozygous mutation, or compound heterozygous mutation; and
2. Patient must have experienced the defined signs and symptoms of SMA type I, II or IIIa prior to 3 years of age (see Notes); and
3. Treatment must be given concomitantly with standard of care for this condition; and
4. Treatment must not exceed four loading doses (at days 0, 14, 28 and 63); and
5. Patient must be 18 years of age or under.

Continuation – spinal muscular atrophy (SMA) – symptomatic type I, II and IIIa
Applications only from, or in consultation with a specialist medical practitioner experienced in the diagnosis and management of SMA associated with a neuromuscular clinic of a recognised hospital in the management of SMA.
Re-assessment required after 12 months

All of the following:

1. Patient must have had a previous approval for nusinersen; and
2. Treatment must be given concomitantly with standard of care for this condition; and
3. There has been demonstrated maintenance of motor milestone function (as assessed using age-appropriate scales: the HINE Section 2, CHOP INTEND, or HFMSE) since treatment initiation; and
4. Treatment must be ceased when invasive permanent assisted ventilation (see Note) is required in the absence of a potentially reversible cause while being treated with this drug.

Notes:
Invasive permanent assisted ventilation means:
Ventilation via tracheostomy tube for greater than or equal to 16 hours per day.

Defined signs and symptoms of type I SMA are:
i) Onset before 6 months of age; and
ii) Failure to meet or regression in ability to perform age-appropriate motor milestones.

Defined signs and symptoms of type II SMA are:
i) Onset between 6 and 18 months; and
ii) Failure to meet or regression in ability to perform age-appropriate motor milestones.

Defined signs and symptoms of type IIIa SMA are:
i) Onset between 18 months and 3 years of age; and
ii) Failure to meet or regression in ability to perform age-appropriate motor milestones.

Discussion

1.5. The Subcommittee noted that an application for nusinersen for the treatment of paediatric patients (18 years or under) with spinal muscular atrophy (SMA) types I, II, or IIIa with symptom onset before three years of age was considered by the Rare Disorders Subcommittee in November 2018. At this time, the Subcommittee recommended that the application be deferred until longer-term follow-up data were published from the SHINE and/or NURTURE trials. PTAC subsequently reviewed the Record of the November 2018 Rare Disorders Subcommittee in February 2019, and agreed with the Subcommittee's recommendation to defer a decision on nusinersen until longer-term follow-up analyses were available.

1.6. The Subcommittee noted that a resubmission for nusinersen was received by PHARMAC in August 2019 which included clarification of proposed eligibility criteria for nusinersen, longer-term data from the SHINE and NURTURE trials, and a revised price offer. The Subcommittee also considered correspondence regarding nusinersen received from a Paediatric Neurologist, Muscular Dystrophy New Zealand, and letters of support from the public.

1.7. The Subcommittee noted that the resubmission requested that the proposed eligibility criteria for nusinersen be widened from the original submission, which was for paediatric patients (18

years or under) with spinal muscular atrophy (SMA) types I, II, or IIIa with symptom onset before three years of age, to include pre-symptomatic individuals who have been genetically diagnosed with SMA.

1.8. The Subcommittee reviewed the aetiology and pathophysiology of SMA. The Subcommittee noted that SMA represents a continuous spectrum of phenotypes that are categorised into SMA type based on clinical manifestations (ie age of symptom onset and motor milestones achieved).

1.8.1. The Subcommittee noted the point raised in the correspondence that individuals with SMA type IIIa do achieve the ability to walk, which differs from the definition described by the Rare Disorders Subcommittee in 2018 (individuals with SMA IIIa are predominantly non-ambulatory). The Subcommittee agreed with the correspondent, noting that individuals with SMA type IIIa do achieve the ability to walk; however, the Subcommittee also noted that these individuals have a high risk of losing this ability and becoming non-ambulatory during youth or adulthood.

1.9. The Subcommittee noted that the phenotypic severity and therefore the type of SMA is, at least in part, modified by the number of copies of the *SMN2* gene. The Subcommittee considered that, in general, individuals with one copy of *SMN2* develop SMA type 1a (also referred to as type 0, fatal in early infancy), individuals with two copies of *SMN2* develop SMA type Ib (feeding and respiratory problems, poor or no cephalic control), and individuals with three copies of *SMN2* can develop SMA of variable disease severity, ranging from type Ic (feeding and respiratory problems, some cephalic control) to SMA type V (ambulatory for normal life-span) (Serra-Juhe & Tizzano. Eur J Hum Genet. 2019; doi: 10.1038/s41431-019-0415-4. [Epub ahead of print]). The Subcommittee noted that individuals with four or five copies of *SMN2* remain ambulatory and independent well into adulthood and have a normal lifespan. The Subcommittee considered that although it is not a perfect prognostic biomarker, the number of *SMN2* copies is the best phenotypic modifier of SMA identified to date.

1.10. The Subcommittee noted that nusinersen is an antisense oligonucleotide therapy that modifies *SMN2* splicing allowing for translation of full-length SMN protein. The Subcommittee noted that nusinersen does not cure SMA but shifts the severity profile towards a milder disease phenotype.

1.11. The Subcommittee noted that the resubmission included a description of the natural history of individuals with SMA type I and SMA type II and III gathered from published literature. The Subcommittee used these data as a point of comparison when considering the benefit reported for nusinersen in the pivotal trials.

1.12. The Subcommittee noted that the resubmission included longer-term follow up data for patients with infantile-onset SMA (most likely to develop SMA type I) from the ENDEAR-SHINE study.

1.12.1. The Subcommittee noted that they had previously considered results from the ENDEAR-SHINE study after a median treatment duration of 528.6 days (30 June 2017 data cut). At the current meeting, the Subcommittee considered data from ENDEAR-SHINE after a median treatment duration of 987 days (15 October 2018 data cut); these results have not been published in a peer reviewed journal at this time, but were presented at the 2019 American Academy of Neurology Annual Meeting (Finkel et al. Interim Report on the Safety and Efficacy of Longer term Treatment with Nusinersen in Infantile onset Spinal Muscular Atrophy (SMA): Updated Results From the SHINE Study. Presented at: 2019 American Academy of Neurology Annual Meeting (AAN). May 4 to 10, 2019; Philadelphia, PA.).

1.12.2. The Subcommittee noted the results of the motor function assessments at the time of the October 2018 data cut of ENDEAR-SHINE, including change in CHOP INTEND (Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders) scores over time and WHO motor milestones. The Subcommittee considered that, in general,

the results indicated a reversal of decline and further improvements in motor function over time with nusinersen treatment, and that greater improvements were observed when nusinersen treatment was initiated at a younger age. The Subcommittee noted that no statistical analyses were provided for these data, which limited the interpretation of the results at this stage.

1.12.3. The Subcommittee noted that 12 of the 24 patients who had received sham control in ENDEAR were alive and without permanent ventilation at baseline in SHINE, and that 7 of 12 of these infants were alive and without permanent ventilation at the time of the October 2018 data cut of ENDEAR-SHINE. The Subcommittee noted the Kaplan-Meier curve for time to death or permanent ventilation presented at the AAN meeting. The Subcommittee noted that the median time to event was 75 weeks in patients previously treated with nusinersen compared with 22.6 weeks for patients who had received the sham control.

1.12.4. The Subcommittee considered that the safety profile was consistent with that previously reported in ENDEAR; the most frequent adverse events were pyrexia and upper respiratory tract infection.

1.13. The Subcommittee noted that the resubmission included longer-term follow up data for pre-symptomatic individuals with SMA (two or three *SMN2* copies) from the NURTURE study.

1.13.1. The Subcommittee noted that they had previously considered results from the NURTURE study after a median treatment duration of 317.5 days (31 October 2016 data cut). At the current meeting, the Subcommittee considered data from NURTURE after a median treatment duration of 1058 days (29 March 2019 data cut); these results were presented at the 2019 Annual Spinal Muscular Atrophy Researcher Meeting (Parsons et al. Nusinersen in Infants Who Initiate Treatment in a Presymptomatic Stage of Spinal Muscular Atrophy (SMA): Interim Efficacy and Safety Results From the Phase 2 NURTURE Study. 30th June 2019. 23rd Annual Spinal Muscular Atrophy Researcher Meeting, 28 to 30 June 2019, Anaheim, CA).

1.13.2. The Subcommittee noted the results of the motor function assessments at the time of the March 2019 data cut of NURTURE, including change in CHOP INTEND scores over time, Hammersmith Infant Neurological Exam (HINE) motor milestone scores over time, and WHO motor milestones. The Subcommittee noted that 80% of children reached the maximum score on the CHOP INTEND scale, 100% (25/25) of children achieved sitting independently, 92% (23/25) walking with assistance, and 88% (22/25) walking alone.

1.13.3. The Subcommittee noted that at the time of the March 2019 data cut of NURTURE, all patients (n = 25; 100%) were alive and none required permanent ventilation (median time to event could not be estimated). The Subcommittee noted that 4 of 25 patients (all with 2 SMN2 copies) required respiratory support during acute reversible illness.

1.13.4. The Subcommittee noted that of the patients included in NURTURE, 72% did not meet the protocol definition of clinically manifested SMA at 24 months of age.

1.13.5. The Subcommittee considered that nusinersen was well tolerated in NURTURE and no new safety signals were identified.

1.14. The Subcommittee noted that the resubmission included longer-term follow up data for childhood-onset SMA (type II or III) from the CHERISH-SHINE study.

1.14.1. The Subcommittee noted that they had previously considered results from the CHERISH-SHINE study after a median treatment duration of 441.5 days (30 June 2017 data cut). At the current meeting, the Subcommittee considered data from CHERISH-SHINE after a median duration of 1175 days (15 October 2018 data cut);

these results were presented at the 2019 American Academy of Neurology Annual Meeting (Darras et al. Interim Report on the Safety and Efficacy of Longer term Treatment With Nusinersen in Later onset Spinal Muscular Atrophy (SMA): Results From the SHINE Study. Presented at: 71st American Academy of Neurology (AAN) Meeting. May 4 10, 2019 | Philadelphia, PA. P063).

1.14.2. The Subcommittee noted the results of the motor function assessments at the time of the October 2018 data cut of CHERISH-SHINE, including change in Hammersmith Functional Motor Scale Expanded (HFMSE) scores and Revised Upper Limb Module (RULM) scores. The Subcommittee considered that the results indicated stabilisation in motor function scores in the majority of patients, as opposed to improvement, with the most gains observed in patients who were younger at treatment initiation (<3.69 years at first dose).

1.14.3. The Subcommittee considered that the safety profile of nusinersen in CHERISH-SHINE was consistent with the known profile of nusinersen.

1.15. The Subcommittee noted that the resubmission also included published long-term follow up data for childhood-onset SMA (type II or III) from the CS2-CS12 studies (mean enrolment 965.1 days; Darras et al. Neurology. 2019;92:e2492-e2506).

1.15.1. The Subcommittee noted the results of the motor function assessments for the CS2-CS12 studies, including HFMSE scores, Upper Limb Module (ULM) scores, and the 6-Minute Walk Test. The Subcommittee considered that the results indicated that motor function was maintained or improved over the treatment duration.

1.15.2. The Subcommittee considered that no new safety concerns were identified in these studies, and most adverse events were of mild or moderate severity.

1.16. The Subcommittee considered that the evidence provided by the clinical trials suggests that treatment with nusinersen improves survival, reduces the risk of ventilation, and maintains motor function in patients with pre-symptomatic and infantile-onset SMA and improves motor function in patients with childhood-onset SMA. The Subcommittee also considered that there is a possibility that improved motor function may be associated with a survival advantage in individuals with childhood onset SMA, but that no updated survival data has been provided for this group.

1.17. The Subcommittee considered that the clinical trials investigating nusinersen are of good strength and quality. The Subcommittee noted that despite the follow-up being limited to a duration of less than four years, the updated data indicates that the treatment response is likely to be durable. The Subcommittee also considered that the magnitude of benefit observed in the clinical trials compared with the natural history of the disease gives confidence that nusinersen is likely to provide a clinically meaningful benefit.

1.18. The Subcommittee considered that the NURTURE trial was a single arm Phase 2 trial and therefore the results are associated with some uncertainty due to trial design; however, the Subcommittee considered that even once statistical analysis and peer review has been completed, the effect size reported in the interim analysis is of such a magnitude that it would be unlikely to significantly change the outcomes.

1.19. The Subcommittee was alerted to a publication by Galziou et al. (BMJ 2007;334:349-51), in which the authors considered that at times very large treatment effects can overwhelm concerns of bias (the relation between a treatment and its effect being sometimes so dramatic that bias can be ruled out as an explanation). The Subcommittee considered this may be the case with nusinersen, particularly in the treatment of pre-symptomatic individuals with spinal muscular atrophy and two or three *SMN2* copies.

1.20. The Subcommittee also noted that the updated data considered at the current meeting, with the exception of Darras et al. Neurology. 2019;92:e2492-e2506, has only been presented at conferences and has not yet been published as peer reviewed scientific articles.

1.21. The Subcommittee considered that the data from the clinical trials suggests that improvements in motor function are more pronounced when treatment is initiated earlier, and that the benefit appears to be greatest in patients treated in the pre-symptomatic stage of SMA. The Subcommittee considered that this is consistent with the pathophysiology of SMA, in which a deficiency in SMN protein leads to irreversible motor neuron degeneration.

1.22. The Subcommittee considered that limiting eligibility for nusinersen to pre-symptomatic individuals with two or three copies of *SMN2* would capture those children most likely to develop SMA type Ib, II, and IIIa. The Subcommittee considered that based on the data from the NURTURE trial described above, that these are the individuals with the most potential to benefit and the highest need of a disease-modifying treatment. However, the Subcommittee considered that patients with symptomatic disease also have a high health need with the potential for significant loss in life potential from disability and early death.

1.23. The Subcommittee noted that at the November 2018 meeting, the Subcommittee had considered that patients with SMA type I and those with SMA type II/IIIa were different SMA populations and could be considered separately. However, at the current meeting the Subcommittee considered that in practice, due to SMA being a spectrum disease, that it would be clinically difficult to treat one patient sub-group and not the other. The Subcommittee considered that if nusinersen was to be funded for symptomatic patients with disease onset before three years of age, that the eligibility criteria should include patients with SMA type I, II, and IIIa, as all patients within these groups would significantly benefit from treatment.

1.24. The Subcommittee considered that it is unclear at this stage whether treatment with nusinersen can be stopped once a patient has achieved an optimal response. Members therefore considered that, unless evidence is provided indicating that further deterioration would not occur should treatment be stopped or interrupted, then it is likely that treatment with nusinersen would be lifelong.

1.25. The Subcommittee considered that there may be a small number of pre-symptomatic patients with three copies of *SMN2* who would go on to develop SMA type IIIb or IV.

1.26. The Subcommittee considered that limiting eligibility for nusinersen to pre-symptomatic patients would require SMA to be included in the newborn screening programme; the validity and implementation of this would need to be investigated if nusinersen was to be funded. One Member also considered that, based on clinical experience, the introduction of newborn screening for a condition frequently results in more than the expected number of patients being identified, and that in the case of SMA this could result in as many as twice as many cases being identified.

1.27. The Subcommittee noted there are a number of gene therapies under development for the treatment of SMA. The Subcommittee noted that the one-time infusion gene therapy onasemnogene abeparvovec-xioi (Zolgensma) was approved by the U.S. Food & Drug Administration for the treatment of SMA earlier this year.

1.28. The Subcommittee noted that the price proposed by the supplier is still very high, resulting in low cost effectiveness for the application. The Subcommittee considered that if nusinersen was to be funded, it would be important for patients to be included in a registry in order for New Zealand specific data to be collected, helping evidence development internationally.

1.29. The Subcommittee considered that, due to the magnitude of benefit reported in the updated analyses from the NURTURE, ENDEAR-SHINE and CHERISH-SHINE trials, that the data was robust enough to inform a recommendation for pre-symptomatic and symptomatic patients. The Subcommittee considered that there is good quality evidence that treatment

with nusinersen improves survival, reduces the risk of ventilation, and maintains motor function in patients with pre-symptomatic and infantile-onset SMA and improves motor function in patients with childhood-onset SMA. The Subcommittee also considered that the greatest benefit is likely to be observed in the pre-symptomatic stage.