Record of the Rare Disorder's and Neurological Combined Subcommittee of PTAC
Meeting held on 05 March 2021

Subcommittee records are published in accordance with the Terms of Reference for the Pharmacology and Therapeutics Advisory Committee (PTAC) and PTAC Subcommittees 2016.

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

The Rare Disorders and Neurological Subcommittees 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.

PTAC Subcommittees make recommendations, including priority, within their therapeutic groups of interest.

The record of this Subcommittee meeting will be reviewed by PTAC at its May 2021 meeting.

PTAC Subcommittees and PTAC may differ in the advice they provide to PHARMAC, including recommendations' priority, due to the committees' different, if complementary, roles, expertise, experience, and perspectives.

PHARMAC is not bound to follow the recommendations made below. Applications are prioritised by PHARMAC against other funding options and progressed accordingly. The relative priority of any one funding choice is dependent on a number of factors, including (but not limited to) the recommendation of PTAC and/or PTAC Subcommittees, the mix of other applications being assessed, the amount of funding available, the success of commercial negotiations and/or the availability of clinical data.

Present from the Rare Disorders Subcommittee:
Tim Stokes (Chair; Chair for combined meeting)
James Cleland
Melissa Copland
Emma Glamuzina
Dylan Mordaunt
Carlo Marra
Katherine Neas (part of meeting)
Humphrey Pullon
Howard Wilson
William Wong

Present from the Neurological Subcommittee:
Giles Newton-Howes (Chair)
John Fink
John Mottershead
Paul Timmings

Apologies:
Brian Anderson
Janice Fletcher
Richard Hornabrook
Mark Weatherall

Summary of recommendations

The following recommendation summary is an order of the discussions held at the meeting.

Pharmaceutical and Indication	Recommendation
• Risdiplam for SMA Type 1	High Priority
• Risdiplam for SMA Type 2 and 3	Defer

1. The role of PTAC Subcommittees and records of meetings

1.1. This meeting record of the Rare Disorders and Neurological Subcommittees of PTAC is published in accordance with the Terms of Reference for the Pharmacology and Therapeutics Advisory Committee (PTAC) and PTAC Subcommittees 2016, available on the PHARMAC website at https://www.pharmac.govt.nz/assets/ptac-terms-of-reference.pdf.

1.2. The Terms of Reference describe, *inter alia*, the establishment, activities, considerations, advice, and the publication of such advice of PTAC Subcommittees and PTAC.

1.3. Conflicts of Interest are described and managed in accordance with section 7.2 of the PTAC Terms of Reference.

1.4. The Rare Disorders and Neurological Subcommittees are Subcommittees of PTAC. The Subcommittees and PTAC have complementary roles, expertise, experience, and perspectives. The Rare Disorders and Neurological Subcommittees and other

PTAC Subcommittees may therefore, at times, make recommendations for treatments for spinal muscular atrophy that differ from PTAC's, including the priority assigned to recommendations, when considering the same evidence. Likewise, PTAC may, at times, make recommendations for treatments for spinal muscular atrophy that differ from the Rare Disorders and Neurological Subcommittees' recommendations, or PTAC Subcommittees may make recommendations that differ from other PTAC Subcommittees'.

1.5. PHARMAC considers the recommendations provided by both the Rare Disorders and Neurological Subcommittees and PTAC and any other relevant PTAC Subcommittees when assessing applications for treatments for spinal muscular atrophy.

2. Risdiplam (Evrysdi) for the treatment of spinal muscular atrophy (SMA), including Types 1-3

Application

2.1. The Subcommittees reviewed a funding application from Roche Products New Zealand for risdiplam (Evrysdi) for the treatment of spinal muscular atrophy (SMA), including Types 1-3.

Recommendation

2.2. The Subcommittees recommended that risdiplam for the treatment of Type 1 spinal muscular atrophy be listed with a **high** priority within the context of treatments for rare disorders and neurology treatments, with the following provisional Special Authority criteria:

> Initial application only from a neurologist or paediatric neurologist. Approvals valid for 12 months for applications meeting the following:
> All of the following:
> 1 Patient has experienced the defined signs and symptoms of SMA Type 1 prior to 6 months of age; and
> 2 Biallelic SMN1 pathogenic mutations detected; and
>
> Renewal only from a neurologist or paediatric neurologist. Renewals valid for 12 months.
> All of the following:
> 1 Patient has confirmed diagnosis of SMA Type 1; and
> 2 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
> 3 Patient does not require ventilation via tracheostomy tube for greater than or equal to 16 hours per day, in the absence of a potentially reversible cause while being treated with this drug.

The Subcommittees noted that the recommended Special Authority criteria are provisional, and that the funding criteria for SMA treatments may continue to evolve with further input from clinical advisors. The Subcommittees noted that the recommended criteria for risdiplam have the same intent as the recommended criteria for nusinersen in the SMA Type 1 group, however that the criteria are worded slightly differently. The differences are due to further refinement of the criteria (which may also be relevant to nusinersen), or alternatively may be risdiplam specific (eg. no requirement for a loading dose due to the treatment regimen).

2.3. The Subcommittees recommended that risdiplam for spinal muscular atrophy Type 2 and 3 within the context of treatments for rare disorders and neurology treatments be **deferred** pending longer follow up analyses from the SUNFISH trial.

Discussion

2.4. The Subcommittees noted spinal muscular atrophy (SMA) is a progressive neuromuscular disease, where the most severe cases are associated with an earlier age of onset, lower achievement of maximal motor milestone development during the patient's lifetime, and a lower life expectancy. The Subcommittees noted that SMA is categorised into 'types' based on age of onset and maximal motor function achieved. The Subcommittees noted that this funding application was in relation to types 1, 2 and 3 only, which includes patients with symptomatic disease diagnosed from birth to the age of 18 years.

2.5. The Subcommittees noted that the severity of disease varies depending on Type of SMA, with symptoms varying from inability to sit or roll (Type 1) to the potential loss of ability to walk over time (Type 3). The Subcommittees noted that the average life expectancy of those with Type 1 SMA is less than two years, while individuals with Type 3 are expected to have an unaffected lifespan.

2.6. The Subcommittees noted that PHARMAC has not previously received a funding application for people with SMA Types 3b and 3c. The Subcommittees noted that people with SMA Type 3b are diagnosed age >3 years, while those with Type 3c are diagnosed between >12 to ≤18 years. The Subcommittee also noted that PHARMAC had not previously received a funding application for treatment for patients with SMA over the age of 18 years.

2.7. The Subcommittees noted the high health need of family, whānau and caregivers of people with SMA. The Subcommittees noted that a small number of families have left New Zealand to seek funded SMA treatment for their children; the Subcommittees acknowledged the significance of this and the enormous impact that this disease has on both the patient and their whānau.

2.8. The Subcommittees noted that there are currently no funded disease modifying treatments for SMA. The Subcommittees noted that supportive care for individuals with SMA includes non-pharmaceutical interventions such as physiotherapy and nutritional support to assist with respiratory, mobility or feeding difficulties. The Subcommittees noted that PHARMAC has previously received and assessed a funding application for nusinersen for pre-symptomatic, Type 1, 2 and 3a SMA. The Subcommittees noted that nusinersen remains an option for investment.

2.9. The Subcommittee noted that PHARMAC has not received any other funding applications for the treatment of SMA, however that other agents such as gene replacement therapy are on the horizon.

2.10. The Subcommittees noted that SMA (Types 1, 2 and 3a) had previously been considered to meet PHARMAC's Rare Disorder Principles. The Subcommittees considered that the application for risdiplam for SMA, Types 1-3 does meet these principles; however, members noted that there are variable reports of SMA incidence and as such it was not unanimously agreed that this application met Principle Two.

2.11. The Subcommittees noted that risdiplam modulates SMN2 gene splicing, binding two sites in SMN2 pre-mRNA, allowing full length SMN mRNA and protein to be synthesised; with systemic distribution demonstrated in both the central nervous system and peripheral organs in vivo. The Subcommittees queried the half-life of risdiplam, noting that such pharmacokinetic aspects could have appreciable effects on dosing frequency, and noted that they would like to review the relevant data.

2.12. The Subcommittees noted the results of FIREFISH (part II), a phase II, open label study of 41 SMA Type 1 patients treated with risdiplam once daily (Servais et al. 73rd Annual Meeting of the American Academy of Neurology. Canada. 2020). The Subcommittee noted that patients were aged one to seven months old (inclusive) at enrolment and had confirmed diagnosis of 5q-autosomal recessive SMA, with two SMN2 gene copies.

2.13. The Subcommittees noted at 12 months that 29% of patients had met the primary outcome, sitting without support for at least five seconds. The Subcommittee also noted at 12 months, 93% of infants were alive, 85% of infants were event free, and 95% of infants alive maintained the ability to swallow.

2.14. The Subcommittees considered that, while relatively short, a 12-month follow up for the SMA Type 1 population was a highly relevant timeframe, noting that Type 1 patients are severely impacted by SMA and sadly often die within this timeframe. The Subcommittee noted that historical controls (also with two SMN2 copies) have a reported median age of event-free survival of 10.5 months (Finkel et al. Neurol. 2014;83:810-7). The Subcommittee considered that the survival benefit of risdiplam demonstrated at 12 months in the FIREFISH study was highly clinically meaningful.

2.15. The Subcommittees noted that 49% of all infants in the FIREFISH study did not require hospitalisation in the 12-month study period. The Subcommittees considered that while this appeared to be a positive finding, it was unclear at this stage whether treatment with risdiplam would have a sustained response in reducing the need for hospitalisation, or whether it would only delay this need.

2.16. The Subcommittees noted that risdiplam was reasonably well tolerated, with the most common adverse event of pneumonia. The Subcommittees noted that there were three reported fatal events in the trial (7%) secondary to SMA-related respiratory complications.

2.17. Members noted that risdiplam has a similar mechanism of action to nusinersen, which has demonstrated sustained effect in people with Type 1 SMA over longer follow up. The Subcommittee therefore considered that overall, despite the short-term follow-up, the evidence for risdiplam in Type 1 SMA was of moderate strength with a large, clinically meaningful effect. The Subcommittee noted that due to the small number of patients and availability of other SMA treatments, it was unlikely that better quality evidence (ie. a sufficiently-powered placebo-controlled randomised control trial) would become available.

2.18. The Subcommittee noted that there was currently no available direct comparison of nusinersen and risdiplam for the treatment of Type 1 SMA. The Subcommittee noted that while small patient numbers make it difficult to accurately compare the two treatments, it considered that with currently available data, it would be reasonable to conclude that risdiplam demonstrates at least the same or similar effect of benefit compared with nusinersen in individuals with Type 1 SMA, with no informal signals of inferiority (although formal testing for non-inferiority has not apparently been undertaken).

2.19. The Subcommittees noted the results of the SUNFISH trial (part II), a phase II randomised (2:1), double-blind, placebo-controlled trial of 180 individuals with SMA Type 2 or non-ambulant Type 3 (Mercuri et al. SMA Europe. France. 2020 (NCT02908685)). Participants had a mean age of onset of 15.5 months, were aged two to 25 years at time of treatment, were able to sit independently and had some upper limb mobility and strength.

2.20. The Subcommittees considered that the SUNFISH trial included a broad population, noting that there were no exclusion criteria related to the degree of scoliosis, contractures, feeding support or non-invasive ventilation.

2.21. The Subcommittees noted a least squares mean change from baseline to 12 months of 1.5 in Motor Function Measure, MFM32, in patients treated with risdiplam compared with placebo (95% confidence interval: 0.3-2.81, P=0.0156). The Subcommittees also noted a greater proportion treated with risdiplam had an improvement of at least three points in MFM32 total score compared with placebo (38% vs 24% respectively; odds ratio=2.35).

2.22. The Subcommittees noted that there was a small improvement in the mean change in Revised Upper Limb Module (RULM) scores in patients treated with risdiplam compared with placebo, shown by a least squares mean change from baseline of 1.61 vs 0.02 (odds ratio=1.59; P=0.0028).

2.23. The Subcommittees noted that there were no statistically significant least square mean changes from baseline in Hammersmith Functional Motor Scale Expanded (HFMSE) or SMA independence measures observed between risdiplam and placebo (adjusted, P=0.3902 and P=0.3902 respectively).

2.24. The Subcommittees noted that the minimal clinically important difference values for functional motor scores commonly used in adults with SMA are approximately two for both the RULM and the HFMSE (Stolte et al. Euro J Neurol. 2020;27:2586–94). The Subcommittee also noted the qualitative results McGraw et al. 2017, which reported that patients and caregivers highly value even small improvements and that meaningful change is relative to the functional ability already achieved (McGraw et al. BMC Neurol. 2017;17:68).

2.25. The Subcommittees noted that pneumonia was the most common significant adverse event (7.5% risdiplam compared with 1.7% placebo), while no fatal events were reported.

2.26. The Subcommittees considered that the SUNFISH trial was of moderate strength of small effect and considered that longer-term follow up data would need to be evaluated.

2.26.1. The Subcommittees considered there was some uncertainty of the long-term, ongoing benefit of risdiplam, particularly in the treatment of Type 2 and 3 SMA, due to limited follow up, noting that SMA is a lifelong condition and to date only one year of follow-up data is available, but also observing that 12 months was a substantial time in the context of low survival as seen in SMA overall.

2.27. The Subcommittees noted that as the two primary studies, FIREFISH and SUNFISH, were in two different SMA populations, it considered it appropriate to consider the health benefits of risdiplam in these two different groups separately.

2.28. The Subcommittees noted that using 12-month data of patients with Type 2 and 3 SMA treated with nusinersen had an approximate 3.5 point increase RULM compared with 1.5 points with risdiplam (noting that the risdiplam trial had wider group of Type 3 subtypes). The Subcommittees considered that this may, in part, be explained by the differences in patient cohorts, ie. In SUNFISH the average age was nine years at study entry vs in the CHERISH study (for nusinersen) with an average age of four and exclusion of patients with scoliosis (Mercuri et al. N Engl J Med. 2018;378:625- 35); noting the marked difference in response according to age at starting treatment.

2.29. The Subcommittees noted that neither the FIREFISH nor SUNFISH results had been published formally and fully at the time of assessment, and as such had not yet undergone rigorous peer-review (especially of methods and statistical methods).

2.30. The Subcommittees considered that those who would benefit most from treatment with risdiplam were individuals who would be treated early and/or with more severe disease. The Subcommittees considered that there was a high health need among patients with SMA Type 0 with the potential for these patients to benefit from SMA treatment the most, however noted that this indication was not included in this funding application. The Subcommittees noted that there was an ongoing study of risdiplam for pre-symptomatic SMA, and that they would welcome a funding application for this indication.

2.31. The Subcommittees noted that risdiplam is administered orally. The Subcommittees considered this to be a very suitable formulation and that it would empower family/ whānau to deliver the medicine at home. Members noted that in comparison to other formulations for other SMA treatments (eg. intrathecal injection), an oral formulation may be more suitable. Members were made aware of anecdotal clinical experience of a possible lack of cultural acceptance of lumbar puncture in Tongan people. The Subcommittees also noted that the oral formulation would be equitably favourable for patients and family/ whānau living in deprived or rural areas.

2.32. The Subcommittees considered that there may be a risk of wastage of risdiplam, for example when bottles were taken home. Members considered that this may need to be factored into the cost of this proposal.

2.33. The Subcommittees noted that risdiplam has not yet been recommended for funding in Australia, Canada, Scotland, or England/Wales.

2.34. The Subcommittees noted that the appropriate comparator for patients with Type 1, 2 and 3 SMA is best supportive care. The Subcommittees considered that motor function, bulbar function, hospitalisation, respiratory function, complications of SMA, ventilation, stamina and fatigue, mortality, and adverse effects of treatment were appropriate outcomes. The Subcommittees considered that health-related quality of life (HRQoL) was not an appropriate outcome yet, as there was currently no available data in relation to risdiplam and because HRQoL is difficult to estimate in infants; the Subcommittees noted it would welcome any such data in further assessment of this application.

2.35. The Subcommittees considered that the supplier patient number estimates seemed reasonable. However, the Subcommittee considered that there may be some uncertainty regarding how accurately patients over the age of 18 could be identified. The Subcommittee noted the patient numbers for Type 1, 2 and 3a provided to PHARMAC by Starship Hospital staff in 2020 and considered that these figures were accurate. Members noted that recent reviews have reported an incidence of SMA up to 1 in 11,000 (Verhaart et al. Orphan J Rare Disord. 2017;12).

2.36. Members noted that new-born screening for SMA is currently under consideration among some health care providers; the Subcommittee considered that the impact of screening on patient numbers is uncertain.

2.37. The Subcommittees noted that the Supplier has assumed in its modelling that Type 2 and 3 patients convert to full health following risdiplam treatment. Members considered that a conversion to full health was not supported by currently available data.

2.38. The Subcommittees considered that, compared with regular intrathecal injection treatment for SMA, oral risdiplam has the potential to reduce health system costs to a greater extent, if the same or similar efficacy was achieved relative to other treatment.