Record of the Rare Disorder's and Neurological Combined Subcommittee of PTAC
Meeting held on 6 July 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 November 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
Katherine Neas
William Wong

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

Apologies:
Carlo Marra
Janice Fletcher
Humphrey Pullon
Howard Wilson
Richard Hornabrook
Mark Weatherall

Summary of recommendations

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

Pharmaceutical and Indication	Recommendation
• Risdiplam for symptomatic SMA Type 2 and non-ambulant Type 3 (aged under 25 years)	High

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 those of 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 updated evidence for a funding application from Roche Products New Zealand for risdiplam (Evrysdi) for the treatment of symptomatic spinal muscular atrophy (SMA), including Types 1-3.

2.2. The Subcommittees noted in March 2021, they recommended risdiplam be funded for SMA Type 1 with a high priority. The Subcommittees deferred making a recommendation for SMA Types 2 and 3, pending longer follow up analyses from the SUNFISH trial.

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

Recommendation

2.4. The Subcommittees recommended that risdiplam for symptomatic spinal muscular atrophy (SMA) Type 2 and non-ambulant Type 3 (aged under 25 years) within the context of treatments for rare disorders and neurology treatments be funded with a **high** priority.

2.5. The Subcommittees reiterated their high recommendation for symptomatic SMA Type 1 in the context of treatments for rare disorders and neurology treatments and recommended it be funded with the following Special Authority criteria for this patient population:

> 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
> > 3 Patient does not require invasive permanent ventilation (≥16 hours per day) or non-invasive permanent (≥16 hours per day) assisted ventilation (breathing support administered via nasal cannula or face mask), in the absence of a potentially reversible cause.
>
> 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 an age-appropriate measurement) since treatment initiation); and
> > 3 Patient does not require invasive permanent ventilation (≥16 hours per day) or non-invasive permanent (≥16 hours per day) assisted ventilation (breathing support administered via nasal cannula or face mask), in the absence of a potentially reversible cause while being treated with this drug.

Discussion

International Recommendations

2.6. The Subcommittees noted since their last meeting that the following recommendations by international medicines assessment agencies regarding the funding of risdiplam had occurred:

2.6.1. The PBAC in Australia recommended that risdiplam be funded for patients with SMA Type 1, 2 or 3a aged ≤18 years at the time of treatment initiation if cost-minimised against nusinersen.

2.6.2. The CADTH in Canada recommended that risdiplam should be reimbursed for the treatment of SMA in patients two months and older only if the specified conditions were met.

2.7. The Subcommittees noted that the recommended funding groups differed between Australia and Canada.

SMA Type 1

2.8. The Subcommittees noted the 24 month data of the FIREFISH trial, an open-label study of risdiplam in patients with SMA Type 1 (N=41) (unpublished). The Subcommittees considered that the updated FIREFISH evidence indicated a sustained meaningful benefit of risdiplam in this patient population.

2.9. The Subcommittees noted that the probability of event-free survival was well maintained in the 12-24 month data (83% at 24 months). The Subcommittee noted this appeared clinically significant relative to the natural history of the disease, where a rapid decline in event free survival is observed.

2.10. The Subcommittees noted that the 12 and 24 month FIREFISH data is not currently published or peer reviewed.

2.11. The Subcommittee noted that a number of New Zealand patients with SMA Type 1 were currently receiving compassionate access to nusinersen from the pharmaceutical company, Biogen. The Subcommittee considered that if risdiplam were funded it may be likely that the majority of these patients would switch from nusinersen to risdiplam. This was because the treatments appeared, based on current evidence, to have comparable efficacy and not to obviously differ in terms of safety. It was also anticipated that orally administered treatment would be preferred over an intrathecally administered treatment. The Subcommittees noted that there was currently no published evidence to support switching between SMA treatments, however a study (JEWELFISH) was underway to investigate this. The Subcommittees considered that advice regarding switching could be sought from relevant paediatric neurologists.

2.12. The Subcommittees noted their previously recommended provisional Special Authority criteria for risdiplam for SMA Type 1.

2.12.1. Members considered that the requirement of specific, specialist motor milestone function tests may present practical issues and would likely require input from a neurologist and specialist physiotherapist. Members considered instead that by restricting the applicants to only neurologists or paediatric neurologists, this would ensure that treatment is appropriately directed. As such, the Subcommittees considered that the renewal criteria should require

demonstrated maintenance of motor milestone function (as assessed using an age-appropriate measurement), in line with the current criteria published by CADTH.

2.12.2. Members noted that in New Zealand, invasive permanent ventilation is generally avoided in this patient population unless there is an overriding reason, for example, from a temporary, reversible cause unrelated to underlying SMA disease progression. As such, the Subcommittees considered that the Special Authority criteria should reflect this widespread avoidance, with renewal only considered if a patient is not receiving invasive ventilation or non-invasive permanent ventilation. The Subcommittees considered that, unfortunately, patients would not be expected to benefit from risdiplam once they required invasive ventilation or non-invasive permanent (≥16 hours per day) assisted ventilation. The Subcommittees noted that patients who were receiving invasive ventilation, awake non-invasive ventilation or had undergone a tracheostomy were excluded from the FIREFISH study. The Subcommittees considered that SMA patients requiring respiratory support, for intercurrent illnesses, in New Zealand are often treated with non-invasive assisted ventilation support. The Subcommittees therefore considered that this should not restrict patients from accessing risdiplam and that this should be reflected in the access criteria.

SMA Types 2 and 3

2.13. The Subcommittees noted the updated 24 month data of the SUNFISH trial, which investigated the use of risdiplam in patients with SMA Type 2 and non-ambulant Type 3, aged 2-25 years (unpublished). The Subcommittees noted that at 12 months, placebo patients were switched to risdiplam. The Subcommittees considered that this updated data indicated a sustained benefit with risdiplam.

2.13.1. The Subcommittees considered that the relative increase in demonstrated upper limb function (RULM, mean change 3 points) was likely to be important for the non-ambulant individuals who received this benefit.

2.13.2. The Subcommittees noted a sustained mean change in 32-item Motor Function Measure (MFM32) scores at 24 months; Members considered that while that change was not a clinically significant improvement, the maintenance of motor function was nonetheless clinically important, noting the decline otherwise observed in the natural history of SMA.

2.14. The Subcommittees noted that the placebo group which switched to risdiplam at month 12 demonstrated a possible small benefit or maintenance at the 24 month mark in 32-item Motor Function Measure (MFM32), Revised Upper Limb Module (RULM) and Hammersmith Functional Motor Scale Expanded (HFMSE) scores, however that the delay in treatment initiation appeared to decrease the ability to benefit from risdiplam. The Subcommittee also noted that in those treated with risdiplam for 24 months, the MFM32 total score change from baseline was considerably more favourable in those aged 2-5 years (mean change 6.55, standard deviation (SD) 5.56), with the benefit reducing markedly the older a patient was when initiated on treatment (18-25 years: mean change -0.19, SD 3.12). The Subcommittees considered these points highlighted the benefit of treating SMA early.

2.15. The Subcommittees reiterated that the evidence for risdiplam in SMA Type 2 and non-ambulant Type 3 was of moderate strength of small effect over a short timeframe. The Subcommittees also noted that neither the 12 or 24 month data for

the SUNFISH trial were published or peer reviewed. However, the Subcommittees considered that risdiplam had a high biological plausibility of benefit when compared against the natural history of SMA.

2.16. At this point in time, the Subcommittees did not recommend Special Authority criteria for the SMA Type 2 and non-ambulant 3 (aged under 25 years) group. The Subcommittees considered that the Special Authority should be developed to align with the patient population in the SUNFISH trial, as this is where strong benefit has been signalled. The Subcommittees also considered that the criteria should be further developed through consultation with relevant clinical experts in this field.

2.17. The Subcommittees noted that the current funding recommendation for nusinersen included patients with type 3a SMA aged 18 years or under, while it was recommended that risdiplam be funded for non-ambulant individuals with type 3 SMA under the age of 25 years. The Subcommittees noted that each of these recommendations reflected the groups included in the relevant clinical trials for each medicine. Members considered whether nusinersen and risdiplam should be recommended for the same patient groups, but made no recommendation on this at this time.

2.18. Members considered that a requirement for individuals with type 3 SMA to be non-ambulant may be inappropriate. Members considered that at the time of symptom onset/ diagnosis, it may be unclear whether a patient with type 3 SMA would become non-ambulant. Members considered that there was adequate evidence suggesting that the earlier a person with SMA is treated, the better the potential outcomes and waiting for a person to potentially progress to the point of non-ambulation to access funded treatment may be unreasonable. Members considered that further research into more clinically appropriate ways to target treatment, while ensuring those in the intended population are those in fact eligible for treatment, would be beneficial.

Cost utility (information for economic modelling purposes)

2.19. The Subcommittees considered that while the 24 month data for risdiplam in Types 2 and 3 signalled continued improvement in contrast to the natural history of SMA, it was unlikely that use of risdiplam would result in a conversion to full health.

2.20. The Subcommittees noted that SMA Type 3 does not affect life expectancy, while people with Type 2 have a reduced average life expectancy, although life expectancy is likely wide-ranging within the Type 2 phenotype. The Subcommittees noted uncertainty in the long-term impact of Type 2 on respiratory muscle weakness and scoliosis, which may underlie the group's compromised life expectancy. The Subcommittees considered that it was unclear whether patients with SMA Type 2 who receive risdiplam would experience an increased life expectancy relative to the natural history of the condition.

2.21. The Subcommittees considered that it would be reasonable, for the purposes of economic analysis, to assume that there were no health sector costs incurred for individuals with SMA Type 4 for much of their life course. However, the Subcommittees noted that patients with SMA Type 4 can experience substantial morbidity after disease onset, including being wheelchair-bound. The Subcommittees noted that there was limited literature regarding the health sector costs for SMA Type 4.

2.22. The Subcommittees considered that individuals with SMA Type 3b and 4 likely do not have comparable health related quality of life, noting that both patient groups have general population life expectancy and that the types differ only in age of onset. Hence, assuming the same degree of morbidity, lifetime health-related quality of life would be on average lower for people with SMA Type 3b, given its earlier onset. Members noted it was difficult to make assumptions regarding the different 'types' of SMA as they are predominantly categorised by age of symptom onset and there is often clinical overlap between subtypes.

2.23. The Subcommittees noted the health utility weights for SMA Types reported by Lloyd et al. 2019 and Chambers et al. 2020. The Subcommittees noted the difference in methodologies and the resulting differences in weights, particularly for Type 3.

2.23.1. Members noted that the study by Lloyd et al. 2019 applied a very large weight to ambulation, in distinguishing between utility weights with different sets of symptoms of SMA Type 3. The Subcommittee considered that the Lloyd et al. 2019 utility weight was an estimate of health-related quality of life for people with SMA Type 1 who had converted to a SMA Type 3 phenotype after responding to treatment. The Lloyd et al. 2019 SMA Type 3 utility was considered a more appropriate estimate in this group, while the Committee noted that Chambers et al. 2020 had estimated a utility weight in patients with a diagnosis of SMA Type 3, which may be more appropriate for people with this diagnosis at onset.

2.24. Members noted that the SUNFISH trial included SMA Type 2 (N=84) and non-ambulant individuals with SMA Type 3 (N=36). The Subcommittees noted that the benefit received from risdiplam was similar between the two subpopulations for some outcomes (eg. MFM32 score). Members noted that ambulant and non-ambulant individuals with SMA have different baseline motor function (Mercuri et al. 2016) and as such it could be assumed that the ability to benefit from risdiplam would differ between ambulant and non-ambulant people with SMA. From this, the Subcommittees considered that the SUNFISH data was not generalisable to ambulant Type 3 individuals. This was reflected in the Subcommittees' recommendation for the particular Type 3 indications.

General

2.25. The Subcommittee noted that the recent, international incidence data of SMA of 0.78 per 10,000 was consistent with previous estimates from Arkblad et al. 2009 and Verhaart et al. 2017 (Dangouloff et al. 2021). The Subcommittees considered that the international reported incidence was very similar to that in New Zealand.

2.26. The Subcommittees noted a letter from a clinician regarding the funding application for risdiplam. The Subcommittees noted that while SMA is divided into subtypes, it has a spectrum of clinical severity and all affected individuals have the same underlying pathological process. The Subcommittees considered the potential impact of 'splitting' access to treatment by SMA subtype. Members considered this was an important issue when considering funding applications for SMA, and recommended that relevant clinical experts be consulted and involved.

2.27. The Subcommittees noted that preliminary, unpublished data of the RAINBOWFISH trial was available. The Subcommittees noted that the RAINBOWFISH trial was an open-label, single arm study investigating the use of risdiplam in infants with genetically diagnosed and pre-symptomatic SMA.

2.27.1. The Subcommittees noted that of the five patients treated with risdiplam for at least 12 months, all five met ‘near maximum’ CHOP-INTEND scores by 4-5 months of age, while 80% (N=4) infants achieved HINE-2 motor milestones.

2.28. The Subcommittees considered that the pre-symptomatic SMA group had the greatest potential to benefit from treatment, and would welcome further data and any funding applications for this patient population.