Record of the Rare Disorders Advisory Committee Meeting held on 7 March 2023

Rare Disorders Advisory Committee records are published in accordance with the Terms of Reference for the Specialist Advisory Committees 2021.

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

The Rare Disorders Advisory Committee 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.

Pharmac Advisory Committees make recommendations, including priority, within their therapeutic groups of interest.

The record of this Advisory Committee meeting will be reviewed by PTAC at an upcoming meeting.

Specialist Advisory Committees 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 Specialist Advisory Committees, the mix of other applications being assessed, the amount of funding available, the success of commercial negotiations and/or the availability of clinical data.

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1. Attendance

Present
Rhiannon Braund Co-Chair
Tim Stokes Co-Chair
Janice Fletcher
Emma Glamuzina
Carlo Marra
Kate Neas
James Cleland

Present for parts of the meeting
Jonathan Bishop (Gastrointestinal Advisory Committee)
Russell Walmsley (Gastrointestinal Advisory Committee)
John Fink (Neurological Advisory Committee)
Lynette Sadlier (Neurological Advisory Committee)

2. Summary of recommendations

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

Pharmaceutical and Indication	Recommendation
• Elosulfase alfa in the treatment of Mucopolysaccharidosis Type IVA (MPS IVA)	High Priority
• Agalsidase alfa and migalastat in the treatment of Fabry disease.	Not Applicable (sought additional advice)
• Teduglutide (Revestive) for the treatment of short bowel syndrome with type III intestinal failure (SBS-IF)	High Priority
• SMA treatments (nusinersen and risdiplam) for the treatment of spinal muscular atrophy (SMA) not funded by the existing funding criteria	High Priority
• Risdiplam (Evrysdi) for the treatment of pre-symptomatic spinal muscular atrophy (SMA)	High Priority
• Onasemnogene abeparvovec in the treatment of pre-symptomatic or type 1 spinal muscular atrophy (SMA)	Deferred

3. The role of Specialist Advisory Committees and records of meetings

3.1. This meeting record of the Rare Disorders Advisory Committee is published in accordance with the Terms of Reference for the Pharmacology and Therapeutics Advisory Committee (PTAC) and Specialist Advisory Committees 2021, available on the Pharmac website at https://pharmac.govt.nz/assets/2021-Specialist-Advisory-Committee-Terms-of-Reference.pdf. The Terms of Reference describe, *inter alia*, the establishment, activities, considerations, advice, and the publication of such advice of Specialist Advisory Committees and PTAC.

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

3.3. The Rare Disorders Advisory Committee is a Specialist Advisory Committee of Pharmac. The Rare Disorders Advisory Committee and PTAC and other Specialist Advisory Committees have complementary roles, expertise, experience, and perspectives. The Rare Disorders Advisory Committee and other Specialist Advisory Committees may therefore, at times, make recommendations for treatments for Rare Disorders 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 Rare Disorders that differ from the Rare Disorders Advisory Committee's, or Specialist Advisory Committees may make recommendations that differ from other Specialist Advisory Committees'.

Pharmac considers the recommendations provided by both the Rare Disorders Advisory Committee and PTAC and any other relevant Specialist Advisory Committees when assessing applications for treatments for Rare Disorders.

4. Therapeutic Group Review

4.1. The Committee noted that the applications that it has previously recommended for decline or given a positive recommendation for funding at previous meetings have since by ranked on the Pharmac Options for Investment list. Members noted that Pharmac staff are in the process of updating its assessments of treatments for Fabry disease (ie agalsidase alfa and migalastat) and these would be given further consideration at this 2023 meeting.

4.2. The Committee noted that an application for alglucosidase alfa for the treatment for adult-onset Pompe disease had been recommended for decline based on the uncertainties regarding survival benefit, modest clinical benefits with regards to ambulation and pulmonary function, and the high proposed cost of the medicine. The Committee noted the high level of unmet health need for people with Pompe disease in New Zealand and that newer treatments were on the horizon. Members noted that they would like to review these treatments at a future meeting once a funding proposal had been received.

4.3. The Committee noted that an application for elosulfase for mucopolysaccha-ridosis (MPS) type IVA had been recommended for decline at the 2018 Rare Disorders Subcommittee meeting based on uncertainty regarding the long-term benefit of treatment and the high proposed cost of the medicine. The Committee noted that the supplier has submitted additional evidence to be considered at this meeting.

4.4. The Committee noted that in February 2020 a decision was made to fund ivacaftor (Kalydeco) for the treatment of people with cystic fibrosis with the G551D mutation (or other class III gating mutations) through an agreement with Vertex Pharmaceuticals Pty Ltd (Vertex). Members noted in December 2022 Pharmac issued a public consultation on a proposal to fund elexacaftor with tezacaftor and ivacaftor (brand name Trikafta) for people aged 6 years and above with cystic fibrosis subject to eligibility criteria and a decision was expected to be announced soon.

4.5. The Committee noted that in December 2022, the decision was made that from 1 January 2023, people aged 18 years and under with pre-symptomatic SMA or symptomatic type I, II or IIIa SMA will be eligible to start funded treatment with nusinersen. The Committee noted that as a part of this decision, the net price for natalizumab (Tysabri), dimethyl fumarate (Tecfidera) and interferon beta-1-alpha (Avonex) was reduced by confidential rebate. Members noted that as a part of the consultation to fund nusinersen Pharmac received feedback to extend funded access to include:

- SMA types IIIb and IIIc (symptomatic after 3 years of age)
- People with any type who are aged 19 years and over
- SMA type IV (adult-onset) aged 19 years and over at symptom onset

4.6. The Committee noted that Pharmac staff were seeking clinical advice on these groups as a part of this meeting's items on nusinersen and risdiplam.

4.7. The Committee noted that in January 2023 Pharmac released a public consultation on a proposal to fund risdiplam from 1 May 2023. The Committee noted that if the proposal were to go ahead as consulted on, risdiplam would have the same access criteria as nusinersen (Spinraza) for the treatment of symptomatic type 1, 2 and 3a SMA for people who start treatment when they are 18 years or younger. The Committee noted that risdiplam in the pre-symptomatic SMA setting is to be considered at this meeting and depending on the recommendation and Medsafe approval, the funding proposal may include this use as well.

4.8. The Committee noted that a funding application for nitisinone for the treatment of tyrosinaemia type 1 has been recommended for funding with a high priority due to the high health need, lack of treatment options, and moderate evidence of benefit. Members noted that currently treatment for tyrosinaemia type 1 is funded via Pharmac's Named Patient Pharmaceutical Application (NPPA) pathway for individuals and considered that a Schedule listing subject to eligibility criteria would be unlikely to grow the target population.

4.9. The Committee noted that an application for teduglutide for type III intestinal failure had been recommended for decline at the 2018 Rare Disorders Subcommittee meeting based on uncertainty regarding the long-term benefit of treatment and the high proposed cost of the medicine. The Committee noted that the supplier has submitted additional evidence to be considered at this meeting.

4.10. The Committee noted that sapropterin[1] is currently funded by Pharmac for people with phenylketonuria who are pregnant or trying to become pregnant and that a funding proposal for patients with PKU at risk of cognitive impairment has been ranked on Pharmac's Options for Investment list. The Committee considered that National Metabolic Unit would need to develop guidelines supporting the implementation of sapropterin if it were to be funded and that these could inform the eligibility criteria.

Other updates relating to rare disorders medicines

4.11. The Committee noted that in May 2021 the decision was made to fund six treatments for people with rare disorders. Members noted that a number of these treatments were already being funded for individuals via NPPA, however, considered by listing them on the Schedule new patients can start their treatments sooner. The Committee noted that there were ongoing supply issues with some of the dietary supplements where there was no single supplier with a New Zealand presence to contract with.

4.12. The Committee noted that from July 2022 funded access to enzyme replacement therapy for Gaucher disease moved from Panel application to standard Special Authority (Pharmac decision notification). The Committee considered that this reduced the administrative burden on clinicians and patients alike, with an extended renewal period and further simplified criteria.

4.13. Members noted that as a part of the decision, Pharmac were able to increase the maximum funded dose of imiglucerase to 30 units/kg every other week, thereby

[1] While sapropterin does not meet Pharmac's definition of a rare disorder medicine, the Committee includes Metabolic Physicians who are best placed to provide advice on this funding proposal.

enabling the alignment of dosing regimens between patients who were successfully transitioned to taliglucerase alfa and those who remained on imiglucerase.

Funded treatments for rare disorders

4.14. The Committee noted that Pharmac continues to provide funding for rare disorders both via the Pharmaceutical Schedule and via its Exceptional Circumstances Framework

4.15. The Committee noted that in its assessment processes, Pharmac's decision-making framework enables it to take into account factors that are particularly relevant to people with rare disorders (ie the health need of patients, their family and wider whānau, and the suitability of existing treatment options)

4.16. The Committee noted that spending on medicines for rare disorders has increased in recent years, as has the number of people accessing these treatments.

4.17. The Committee noted the list of medicines listed on the Pharmaceutical Schedule and funded specifically for the treatment of rare disorders. The Committee considered that the eligibility criteria for a number of metabolic agents were due for review as their use has evolved with experience. This included idursulfase, carglumic acid, and alglucosidase alfa (higher dosing needed for infantile Pompe disease).

4.18. The Committee noted that funded sodium benzoate liquid and sodium phenylbutyrate granules were suitable for a limited number of people and that a tablet presentation would be more suitable for most people.

4.19. The Committee noted that there have been issues with securing stock of several brands of levocarnitine liquid.

NPPA review

4.20. The Committee noted an overview from Pharmac staff about NPPA applications for individuals with rare disorders. NPPA provides a more flexible pathway to consider the funding of medicines for individuals who have exceptional clinical circumstances. Members considered that this was useful for identifying potential medicines that could be considered for listing in the Pharmaceutical Schedule.

Horizon scanning

4.21. The Committee noted that phase 3 clinical trials have been completed for avacopan for the treatment of the rare condition of ANCA-associated vasculitis, which affects 1 in 50,000. The Committee noted that the supplier (Vifor Pharma Pty Ltd) has advised Pharmac that it is currently seeking regulatory approval in Australia.

4.22. The Committee noted that there are a number of people enrolled in investigational trials underway using the CRISPR/Cas9 gene-editing platforms in New Zealand. The Committee noted a trial investigating gene therapy for Transthyretin Familial Amyloidosis (FAP). The Committee noted that FAP is characterised by abnormal build-up of amyloid protein in the body's organs and tissues.

4.23. The Committee noted that cerliponase alfa is approved in other jurisdictions and is used to slow the loss of ambulation in symptomatic paediatric patients 3 years of age and older with late infantile neuronal ceroid lipofuscinosis type 2.

4.24. The Committee noted that vosoritide for the treatment of achondroplasia was recommended by the PBAC in November 2022, however, that it is unclear whether this would meet Pharmac's rare disorders principles, given the estimated prevalence of achondroplasia of 1 in 20,000 live births.

4.25. The Committee noted that valoctocogene roxaparvovec, a gene therapy for Haemophilia A, was recently approved by the European Commission and is under evaluation by the FDA.

4.26. The Committee noted that there were newer and more effective enzyme replacement therapies for the treatment of Pompe disease, for example avalglucosidase alfa-ngpt. The Committee considered that it would be worthwhile reviewing Pompe disease and any associated proposals as a disease area.

4.27. The Committee noted that it was aware that patisiran (sold under the brand name Onpattro) was available in other countries for treatment of polyneuropathy in people with hereditary transthyretin-mediated amyloidosis.

Therapies for rare disorders being reviewed by other Committees

4.28. The Committee noted that Pharmac has received a proposal for eculizumab for the treatment of atypical hemolytic uremic syndrome (aHUS) and that this was being referred to the March 2023 Nephrology Advisory Committee meeting.

4.29. The Committee noted that a proposal for voretigene neparvovec, a gene therapy for the treatment of inherited retinal dystrophy, was reviewed by PTAC in February 2023 with the records of this meeting in development.

4.30. The Committee noted that tifamidis (Vyndamax) had been previously recommended for funding with a medium priority by the Cardiovascular Advisory Committee. The Committee noted that there is no approved product available in New Zealand. The Committee noted that they had previously reviewed this application and considered that did not meet Pharmac's definition of a rare disorder and as such, does not meet Pharmac's meet the principles required to enable assessed in lieu of Medsafe approval.

Other Pharmac updates

4.31. The Committee noted that Pharmac had received a consumer application to fund burosumab (brand name Crysvita) for the treatment of X linked hypophosphataemia (XLH). The Committee considered that it was unclear whether this would fall within Pharmac's rare disorders policy based in an approximate incidence of 1 in 20-25,000 individuals. The Committee noted that the Endocrine or Nephrology Specialist Advisory Committees would be better placed to provide clinical advice on the application.

4.32. The Committee noted that trientine hydrochloride is funded for Wilson's disease through NPPA for community-based patients for who penicillamine and zinc are not tolerated. The Committee noted that Pharmac are still working towards achieving schedule listing for this product.

4.33. The Committee noted the recommendations from the Independent Pharmac Review and the work underway at the Ministry of Health to develop a Rare Disorders Policy. The Committee considered that Pharmac should work closely with the Ministry and Te Whatu Ora to identify areas where the agencies can work together to address the ongoing challenges facing people with rare disorders.

5. Elosulfase alfa for the treatment of mucopolysaccharidosis type IVA

Application

5.1. The Advisory Committee reviewed the application for elosulfase alfa in the treatment of Mucopolysaccharidosis Type IVA (MPS IVA).

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

Recommendation

5.3. The Advisory Committee **recommended** that elosulfase alfa for the treatment of MPS IVA be listed with a **high priority** for children under the age of 2 years, within the context of treatments for rare disorders, subject to the following Special Authority Criteria:

Initial application only from a metabolic physician. Approvals valid for 12 months for applications meeting the following criteria.
All of the following:
1. Child has a confirmed diagnosis of mucopolysaccharidosis type IVA; and
2. Child must not have another life threatening or severe disease where the prognosis is unlikely to be influenced by enzyme replacement therapy (ERT) or might be reasonably expected to compromise a response to ERT; and
3. Elosulfase alfa to be administered at a dose of 2 mg/kg weekly.

Renewal only from a metabolic physician. Approvals valid for 12 months for applications meeting the following criteria:
All of the following:
1. The treatment remains appropriate, and the child is benefitting from treatment; and
2. Child has not developed another life threatening or severe disease where the long term prognosis is unlikely to be influenced by ERT; and
3. Child has not developed another medical condition that might reasonably be expected to compromise a response to ERT.

5.4. The Advisory Committee **recommended** that elosulfase alfa for the treatment of MPS IVA be listed with a **medium priority** for individuals aged 2 years and over, within the context of treatments for rare disorders, subject to the following Special Authority Criteria:

Initial application only from a metabolic physician. Approvals valid for 12 months for applications meeting the following criteria.
All of the following:
1. Person has a confirmed diagnosis of mucopolysaccharidosis type IVA; and
2. Either:
   2.1. Person is aged between 2 and 6 years; or
   2.2. If the person is over 6 years of age, they must have a lung capacity Forced Vital Capacity of ≥0.3 litres; and
3. Person must not have another life threatening or severe disease where the prognosis is unlikely to be influenced by enzyme replacement therapy (ERT) or might be reasonably expected to compromise a response to ERT; and
4. Elosulfase alfa to be administered at a dose of 2 mg/kg weekly.

Renewal only from a metabolic physician. Approvals valid for 12 months for applications meeting the following criteria:
All of the following:
1. The treatment remains appropriate, and the person is benefitting from treatment; and
2. Person has not developed another life threatening or severe disease where the long term prognosis is unlikely to be influenced by ERT; and
3. Person has not developed another medical condition that might reasonably be expected to compromise a response to ERT.

5.5. In making these recommendations the Committee considered that:

- Children aged <2 years have higher capacity to receive long term treatment benefit
- Trial data published since November 2018 has reported sustained improvement in lung function and activities of daily living in individuals with MPS IVA treated with elosulfase alfa when functional decline would be expected without treatment.

- Individuals with MPS IVA, and their families and whānau, have severe unmet health need, and elosulfase alfa is the only treatment currently available for this indication;
- Impacts on health services and costs are high, in the absence of funded effective disease treatments, where the current management of patients with MPS IVA is focused on addressing the symptoms of the disease.
- International guidelines recommend treatment with elosulfase alfa, and there here is no other specific therapy for treating this condition.

Discussion

Māori impact

5.6. The Committee discussed the impact of funding elosulfase alfa for the treatment of MPS IVA on Māori health areas of focus and Māori health outcomes. The Committee noted that MPS IVA is not identified as one of the Māori health areas of focus for Pharmac, and considered there is no evidence that MPS IVA disproportionately affects any population groups experiencing health inequities in New Zealand.

Background

5.7. The Committee noted that the Rare Disorders Subcommittee (RDAC) (previously known as the Subcommittee, and now the Rare Disorders Advisory Committee) reviewed this application in November 2018 and recommended that the application be declined based on uncertainty regarding the long-term benefit of treatment and the high proposed cost of the medicine. The Committee also noted that in February 2019, PTAC accepted the recommendation of the Rare Disorders Subcommittee that the funding application be declined.

5.8. The Committee noted that the key evidence reviewed in November 2018 included the following clinical trials:

- **BMN110-502** (Bhattacharya et al. J. Inborn Errors Metab. Screen. 2020(8):1-9)**:** A phase III, open-label, single arm, multicentre trial in Australian participants. All participants given 2mg/kg elosulfase alfa weekly.
- **MOR-004** (Hendriksz et al. Molecular Genetics and Metabolism. 2015;114:178-185): A phase III, randomised, double-blind, placebo-controlled multinational trial. Participants randomised 1:1:1 to receive elosulfase alfa 2mg/kg/week, elosulfase alfa 2mg/kg/every other week, or placebo.
- **MOR-005** (Hendriksz et al. Journal of Inherited Metabolic Disease. 2016;39:839-847): A phase III, open-label trial, which is still ongoing (an extension of MOR-004) where participants initially randomised to either elosulfase alfa regimen in MOR-004 remained on their regimen and placebo participants were re-randomised to one of the two regimens
- **MOR-007** (Jones et al. Pediatric Research. 2015;78:717-722): A phase II, open-label, single arm, multinational trial. Participants aged <5 years received elosulfase alfa 2.0 mg/kg/week.
- **MOR-008** (Burton et al. American Journal of Medical Genetics. 2015;167A:2272-2281): Preliminary results from a randomised, double-blind, pilot study. Participants randomised to elosulfase alfa 2mg/kg/week or 4mg/kg/week.

5.9. At the November 2018 meeting, the then Subcommittee had considered that the evidence for elosulfase alfa for MPS IVA was of low to moderate strength and quality and considered it unclear whether the results observed in the clinical trials translated

to meaningful long-term clinical improvements. The Subcommittee considered that at the time there was significant uncertainty regarding whether elosulfase alfa would provide substantial long-term benefit in all patients with MPS IVA, due to the heterogeneity of the disease and variable age at treatment onset.

Health need

5.10. The Committee noted that MPS IVA, also known as Morquio A syndrome, is a rare, severe, and debilitating inherited disorder caused by mutations of the gene that codes for the lysosomal enzyme N-acetylgalactosamine-6-sulfatase (GALNS), which is an enzyme that degrades glycosaminoglycans (GAGs) including keratan sulfate (KS) and chondroitin-6-sulfate (C6S). The Committee noted that with insufficient GALNS, GAGs and other secondary storage compounds progressively accumulate in multiple body organs and tissues.

5.11. The Committee considered that there is a wide spectrum of disease severity associated with MPS IVA. The Committee noted that the severe clinical manifestations of MPS IVA may lead to premature death (with a mean age of death reported to be 25.3 +/- 17.4 years (Lavery et al, JIMD Rep. 2015;15:59-66). The Committee considered that these early deaths commonly occur from cardio-respiratory complications (obstructive and restrictive lung disease) and central nervous system complications relating to cervical spinal cord compression.

5.12. The Committee noted that there are currently 5 diagnosed cases of MPS IVA in New Zealand. The Committee considered it was possible, but unlikely, that there were more prevalent cases, as individuals with MPS IVA are unlikely to remain undiagnosed due to the severity of their symptoms. The Committee considered that MPS IVA does not disproportionately affect any specific ethnic group.

5.13. The Committee noted that the severe morbidity associated with MPS IVA relates to profound skeletal dysplasia, which commonly results in short stature (most are less than 1 metre tall), abnormalities of the spine, chest and limbs, and cardio-respiratory compromise. The Committee noted that the skeletal dysplasia, short stature, and joint abnormalities as well as impaired respiratory function contribute to patients' restricted mobility.

5.14. The Committee noted that current management of patients with MPS IVA is focused on addressing the symptoms of the disease, often including orthopaedic operations and analgesic medication for musculoskeletal symptoms and complications. Vaccination and aggressive treatments against respiratory infections are recommended, and respiratory surgeries including tonsillectomy are frequently required. (Hendriksz et al. Am J Med Genet A. 2015;167:11-25.

5.15. The Committee considered that there may be a health need for other people as a result for caring for patients with MPS IVA. The Committee considered that the severe health needs of individuals with MPS IVA are likely to have a high emotional and psychological impact on their families and there a likely associated considerable strain on caregivers. The Committee noted one study that explored quality of life for carers of people with MPS that concluded caregivers may face strains (such as attending medical appointments with individuals with MPS IVA, and assisting with daily tasks such as toileting, dressing, or travelling to school or work) which affect their health and well-being (Guarany et al. J Inborn Errors Metab Screen. 2015;3).

5.16. The Committee noted that learning ability and cognitive intelligence of individuals with MPS IVA is not impacted by their condition. The Committee considered that ensuring that these individuals receive adequate education and have the opportunity to take part in meaningful work and other daily activities can be difficult due to MPS IVA-associated barriers.

5.17. The Subcommittee considered that the funding application for elosulfase alfa met Pharmac's principles for rare disorders (Pharmac-applied definition of a rare disorder).

5.18. The Committee considered that MPS IVA does not disproportionately affect any population groups affected by health inequities in New Zealand. The Committee noted that MPS is not identified as one of the Māori health areas of focus for Pharmac.

Health benefit

5.19. The Committee noted that Vimizim is a formulation of elosulfase alfa, which is a purified human enzyme produced by recombinant DNA technology. The Committee noted that elosulfase alfa is intended to provide the exogenous enzyme N-acetylgalactosamine-6-sulfatase that will be taken up into the lysosomes and increase the catabolism of the GAGs, KS and C6S. The Committee noted that cell uptake of elosulfase alfa into lysosomes is through cation independent mannose-6-phosphate receptor mediated internalisation leading to restored GALNS activity and clearance of KS.

5.20. The Committee noted that Vimizim is approved by Medsafe for the treatment of MPS IVA; Morquio A syndrome in children and adults of all ages. The Committee noted that the recommended dosage of elosulfase alfa is 2 mg/kg of body weight administered via intravenous infusion once a week, and that the total volume of the infusion should be delivered over no less than 4 hours.

5.21. The Committee considered that treatment should start as early as possible after diagnosis, ideally before the appearance of non-reversible clinical manifestations of the disease. The Committee noted that MPS IVA is a chronic condition, and considered that treatment with elosulfase alfa would continue for an indefinite length of time.

5.22. The Committee considered that enzyme replacement therapy for MPS IVA has been used internationally for several years. The Committee noted data from the multicentre, multinational, observational Morquio A Registry Study (MARS)which provides 6-year treatment data for elosulfase alfa for MPS IVA (Mitchell et al. Mol Genet Metab. 2022;137(1-2):164-72). The Committee noted the MARS data included 323 patients across 65 clinical sites in 17 countries. The Committee noted the mean age at treatment initiation was 14 years, and that the mean length of treatment exposure was 5.5 years.

5.23. The Committee noted that the MARS study reported that the mean change from baseline for the six-minute walk test (6MWT) was -6.1 metres (95% CI: −27.6, 15.5) over 5.5 years. The Committee considered this a slower decline than what would be expected in an untreated cohort. The Committee considered the effect size less precise with confidence intervals that were wide, but considered there was an indication that people may walk more and could improve their cardiovascular fitness, which may improve their ability to compete daily activities such as getting the bus to school.

5.24. The Committee noted the MARS registry study results for effect of elosulfase alfa on respiratory function as the mean forced expiratory volume in 1 second (FEV1) changing 0.2L from baseline (95% CI: 0.1, 0.2) and the mean forced vial capacity (FVC) changing 0.3L from baseline (95% CI: 0.2, 0.3) across a mean treatment duration 5.7 years (Mitchell et al. Mol Genet Metab. 2022;137(1-2):164-72). The Committee noted that elosulfase alfa appeared to improve both obstructive and restrictive respiratory function. The Committee considered that there may represent an effect on the soft tissues of the ribs and on the airways and lung tissue.

5.25. The Committee also noted a review by Lee et al. (Drug Des Devel Ther. 2022;1:143-54), which included expert commentary on the use of elosulfase alfa for MPS IVA. The Committee noted reported associations between low enzyme activity and disease being severe, and between starting treatment a young age (preferably under the age of two years) and individuals with MPS IVA growing taller than would be expected in untreated individuals. The Committee considered this may be early evidence supporting starting treatment with elosulfase alfa early may lead to individuals with MPS growing taller. The Committee considered that benefits associated with growing taller include improved thoracic growth and ability to exercise (due to improved respiratory function) and participation in the community. The Committee noted that more mild phenotypes are often diagnosed later. Members reiterated that the ideal time to treat is as soon as possible after diagnosis.

5.26. The Committee also considered the following further studies or study final reports, not considered previously by the Committee, also related to the treatment of MPS IVA with elosulfase alpha:

- **MOR-002** (Hendriksz et al. Molecular Genetics and Metabolism. 2018;123:479-487): An open label, single arm phase I/II dose-escalation study. Elosulfase alfa was given at increasing doses over three consecutive 12-week intervals, at doses of 0.1mg/kg, 1mg/kg and 2mg/kg weekly, then 1mg/kg weekly.
- **MOR-100** (Hendriksz et al. Journal of Inherted Metabolic Disorders. 2014;37:979-90): A Phase 3, double-blind, randomised placebo-controlled study. Participants were randomised to elosulfase alfa 2mg/kg fortnightly, elosulfase alfa 2mg/kg weekly, or placebo.
- **MOR-006** (Harmatz et al. American Journal of Medical Genetics. 2017;173:375-383): A Phase 2, open-label study. Participants were treated with elosulfase alfa 2mg/kg weekly.
- **MOR-008** (Treadwell et al. Journal of Inborn Errors of Metabolism. 2017;5:1-5; Berger et al. Journal of Medical Informatics and Decision Making. 2017;42:9-17): Final results of the MOR-008 randomised, double-blind, pilot study, whose early results were considered by the Subcommittee in 2018. Participants received treatment with elosulfase alfa at 2mg/kg/week or 4mg/kg/week.

5.27. The Committee considered that the additional data/information provides evidence of longer-term benefit that was not available when they previously reviewed the application.

Suitability

5.28. The Committee considered that if the infusion was able to be given at home once the individual is stable on therapy, caregivers and individuals with MPS IVA would not be required to attend weekly 4-hour hospital infusion appointments. The Committee considered that weekly four-hour long infusions in a hospital inpatient or other clinical setting may be an additional stressor for some individuals being treated and for those caring for them.

Cost and savings

5.29. The Committee noted that the application to Pharmac estimated the median weight of patients to be 22kg at age 21.4 years. The Committee noted that the MARS registry data reported median weight to be 30kg. The Committee recommended that the calculations for cost be varied to account for these weight differences.

5.30. The Committee considered that if treatment is initiated before two years of age, and there is consequent treatment-induced growth of the spine, the need for orthopaedic surgery may be reduced.

Summary for assessment

5.31. The Advisory Committee considered that the below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for elosulfase alfa if it were to be funded in New Zealand for MPS IVA. This PICO captures key clinical aspects of the proposal and may be used to frame any future economic assessment by Pharmac staff. This PICO is based on the Advisory Committee's assessment at this time and may differ from that requested by the applicant. The PICO may change based on new information, additional clinical advice, or further analysis by Pharmac staff.

Population	Individuals with MPS IVA who have no complications or medical conditions that would interfere with treatment with elosulfase alpha
Intervention	Elosulfase alfa to be administered at a dose of 2 mg/kg weekly
Comparator(s) (NZ context)	Standard care
Outcome(s)	Improved exercise endurance, respiratory function, and ability to perform daily activities. Improved growth potential if treatment commenced before two years of age.
Table definitions: **P**opulation: The target population for the pharmaceutical, including any population defining characteristics (eg line of therapy, disease subgroup) **I**ntervention: Details of the intervention pharmaceutical (dose, frequency, treatment duration/conditions for treatment cessation). **C**omparator: Details the therapy(s) that the patient population would receive currently (status quo – including best supportive care; dose, frequency, treatment duration/conditions for treatment cessation). **O**utcomes: Details the key therapeutic outcome(s), including therapeutic intent, outcome definitions, timeframes to achieve outcome(s), and source of outcome data.	

6. Agalsidase alfa and migalastat in the treatment of Fabry disease

Application

6.1. The Advisory Committee reviewed the applications for agalsidase alfa and migalastat in the treatment of Fabry disease.

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

Recommendation

6.3. The Advisory Committee affirmed its previous **recommendation** that agalsidase alfa be listed within the context treatments for rare disorders for the treatment of Fabry disease, based on high health need, a lack of alternative treatment options, and low-to-moderate level of evidence, including evidence of real-world benefit, subject to the following Special Authority criteria, slightly modified from the previous discussion (additions in **bold**):

Special Authority for Subsidy
Initial application –from **any** relevant **practitioner**. Approvals valid for 12 months for applications meeting the following criteria:
All of the following:

1. The person has been diagnosed with Fabry disease confirmed by demonstration of deficiency of alpha-galactosidase enzyme activity in blood or white cells and/or the presence of a pathogenic *GLA* variant known to result in deficiency of alpha-galactosidase enzyme activity and
2. Any of the following:
    - 2.1. Person has renal disease as defined as:
        - 2.1.1. abnormal albumin (>20 ug/min from at least 2 measurements more than 24 hours apart; male only); and/or
        - 2.1.2. albumin: creatine ratio higher than the upper limit of normal (2 separate measurement, 24 hours apart; males only); proteinuria (>150 mg/hours in male and >300 mg/24 hours in females with clinical evidence of progression); and/or
        - 2.1.3. disease caused by long-term glycosphingolipids deposition in the kidneys; or
    - 2.2. Person has Fabry-related cardiac disease: left ventricular hypertrophy (determined by MRI or ECG) and/or arrhythmia or conduction defect; or
    - 2.3. Person has ischaemic vascular disease: determined on objective measures; or
    - 2.4. Person has uncontrolled chronic pain despite use of appropriate doses of analgesic/antiepileptic medications; or
    - 2.5. Person has uncontrolled Fabry related gastrointestinal symptoms as defined by the gastrointestinal symptom rating scale (GSRS) despite the use of other therapeutics; or
    - 2.6. Person has significant health-related quality of life limitations due to Fabry disease as assessed by a metabolic medicine specialist

Renewal –from **any** relevant **practitioner** ~~specialist~~. Approvals valid for 12 months for applications meeting the following criteria:
All of the following:

1. The treatment remains appropriate, and the person is benefitting from treatment.

6.4. The Advisory Committee affirmed its previous **recommendation** that migalastat be listed within the context treatments for rare disorders and possible funding of enzyme replacement therapy for the treatment of Fabry disease subject to the following Special Authority criteria, slightly modified from previous discussions (additions in bold):

Special Authority Criteria
Initial application –from **any** relevant specialist . Approvals valid for 12 months for applications meeting the following criteria:
All of the following:

1. The person has been diagnosed with Fabry disease confirmed by demonstration of deficiency of alpha-galactosidase enzyme activity in blood or white cells and/or the presence of genetic mutations known to result in deficiency of alpha-galactosidase enzyme activity; and.
2. Person must be genotyped to determine if they have an amenable *GLA* mutation*; and
3. Any of the following:
    - 3.1. Person has renal disease:
        - 3.1.1. Abnormal albumin (>20 ug/min from at least 2 measurements more than 24 hours apart; male only); and/or
        - 3.1.2. Albumin: creatine ratio higher than the upper limit of normal (2 separate measurement, 24 hours apart; males only); and/or
        - 3.1.3. Proteinuria (>150 mg/hours in male and >300 mg/24 hours in females with clinical evidence of progression); and/or
        - 3.1.4. Disease caused by long-term glycosphingolipids deposition in the kidneys; or
    - 3.2. Person has Fabry-related cardiac disease as determined by cardiac MRI, echocardiogram or ECG
    - 3.3. Person has ischaemic vascular disease: determined on objective measures; or
    - 3.4. Person has uncontrolled chronic pain despite use of analgesic/antiepileptic medications; or
    - 3.5. Person has uncontrolled Fabry related gastrointestinal symptoms as defined by the gastrointestinal symptom rating scale (GSRS) despite the use of other therapeutics; or
    - 3.6. Person has significant health-related quality of life limitations due to Fabry disease as assessed by a metabolic medicine specialist

Renewal –from **any** relevant **practitioner** ~~specialist.~~ Approvals valid for 12 months for applications meeting the following criteria:
All of the following:

1. The treatment remains appropriate, and the person is benefitting from treatment.

Note: *The Galafold Amenability Table (www.galafoldamenabilitytable.com) is an online search tool that provides a list of GLA mutations currently known to be amenable or not amenable to treatment with migalastat.

Discussion

Patient lived experience

6.5. A family living with Fabry disease shared their experience with the Rare Disorders Advisory Committee and Pharmac staff. The Committee and Pharmac staff valued this opportunity and considered that a different perspective helped to frame the Committee's discussions.

6.6. Family members recounted the burden that Fabry disease placed on their individual lives and on their broader family situation. The family talked about the ways by which Fabry disease can limit an individual's ability to participate fully in day-to-day life and to plan for the future.

6.7. Family members described the grief and trauma associated with a hereditary disease where multiple members of the family are affected, particularly where there are no effective treatment options available to them.

6.8. Family members expressed concern about future children/grandchildren inheriting the disease and potential inadequate access to treatments for these generations.

6.9. Members of the family explained that some of them living in Australia are unable to return to New Zealand without having to give up access to enzyme replacement therapy they are receiving in Australia.

6.10. Other members of the family shared they will also need to leave for Australia, with their immediate family, to access enzyme replacement therapy and the repercussions of leaving their wider family, friends, business and community behind.

6.11. Members of the family shared their personal experience accessing enzyme replacement therapy. They described a reduction their overall symptom burden and explained that treatment had changed their long-term outlook, giving them a renewed sense of hope. Family members explained that this made it even more difficult to witness the decline in health of family members still based in New Zealand.

6.12. The family thanked the Committee for the opportunity to present and hoped that their experience with Fabry disease would inform further discussion.

Māori impact

6.13. The Committee discussed the impact of funding agalsidase alfa and migalastat for the treatment of Fabry disease on Māori health areas of focus and Māori health outcomes. The Committee noted that genetic testing occurs less frequently in Māori and therefore genetic variants that are more common in Māori may not be identified. In addition renal and cardiac impairments may be misdiagnosed as other health conditions eg. essential hypertension or type 2 diabetes. The Committee considered that Māori were not apparently overrepresented in those with Fabry identified disease, but noting potential barriers to accessing health services including referral to metabolic services with delays in diagnosis/ treatment.

Background

6.14. The Committee noted it had previously considered applications for agalsidase alfa and migalastat.

6.15. The Committee recommended in November 2018 that agalsidase alfa be funded with a medium priority for the treatment of Fabry disease based on high health need, a lack of alternative treatment options, and low-to-moderate level of evidence, including non-randomised cohort study comparative evidence of benefit, subject to the Special Authority criteria.

6.16. The Committee recommended in September 2019 that migalastat be funded with a medium priority following a resubmission by the supplier which addressed concerns regarding the long term effectiveness and treatment costs. The Committee agreed that migalastat should only be considered for funding in the context of enzyme replacement therapy potentially being funded for Fabry disease.

6.17. Following the recommendation in September 2019, Pharmac sought additional advice from the Committee in relation to funding both therapeutics for the treatment of Fabry disease.

Health need

6.18. The Committee noted that Fabry disease is an X-linked sphingolipidosis, caused by complete or partial deficiency of the glycohydrolase α-galactosidase A (α-gal A). Enzyme deficiency results in the accumulation of globotriaosylceramide (Gb3, also known as ceramide trihexoside), as well as digalactosyl ceramide and blood group B, B1, and P1 glycolipids in the lysosomes of vascular endothelial, smooth muscle, epithelial, and ganglion cells.

6.19. The Committee noted incidental commentary in the Branton et al. Medicine (Baltimore). 2002;81:122-38 longitudinal follow-up study, describing how major sites of storage of Gb3 and globotriaosylsphingosine (lysoGb3) include vascular endothelial and smooth muscle cells, peripheral neurons in autonomic and dorsal root ganglia, cardiomyocytes, kidney epithelial cells (podocytes, parietal layer of glomerular capsule, tubular epithelium) and endothelial cells, which can lead to inflammation, proliferation, and fibrosis

6.20. The Committee considered the Spada et al, Am J Hum Genet. 2006;79:31-40 study of newborn infants screened in Italy, which reported a prevalence of 1 in 40,000-117,000 males, which could be as high as 1 in 3100 if late-onset disease is included.

6.21. The Committee noted that Fabry disease is inherited on the X chromosome and thus clinically affects males more frequently and severely than females. The Committee noted the Ortiz et al. Mol Genet Metab. 2018;123:416-27 treatment recommendations, which outlined the typical diagnosis for males, whereby enzyme activity was measured in white blood cells, dried blood spots and fibroblasts. In the classic form of Fabry disease there was less than 1% enzyme activity. The Committee noted that in the common Taiwanese variant of Fabry disease, people can have borderline levels of enzymatic activity. In females with Fabry disease, the disease is more molecular in pathology, with at least 40% of symptomatic heterozygotes maintaining normal to slightly low α-gal A activity. Other biochemistry such as plasma and urine can be used to test of Gb3 and lysoGb3 levels. In females with late onset variants of Fabry disease these levels may also appear in normal range. Other methods of diagnosis include immunohistology of affected tissues.

6.22. The Committee noted that >900 variants reported in the GLA gene, which can limit the genotype-to-phenotype correlation. Later onset/atypical (missense or splicing variants) variants can include the “cardiac variant” pAsn215Ser (pN215S) – whereby left ventricular hypertrophy or hypertrophic cardiomyopathies are typically diagnosed

after 50 years. Other gene mutations linked to phenotypes include the cardiac or classical phenotypes linked with p.Arg112His, p.Arg301Gln, p.Gly328Arg and asymptomatic or disease causing pAsp313Tyr. The IVS4+919G>A mutation has been identified in individuals with Taiwanese ancestry.

6.23. The Committee noted that women who present with heterozygous Fabry disease are variably affected, and clinical manifestations of the disease can present 10 years after males who are affected. The Committee noted that disease course can vary depending on gender, environment and GLA variant.

6.24. The Committee members were made aware that Fabry disease affects multiple systems and is quality of life limiting. This includes pain which manifests as small fibre neuropathy, episodic acroparasthesiae (painful numbness, burning and tingling of the extremities) and pain crises which the Committee noted were often referred to as 'Fabry days', as well as extreme fatigue. Gastrointestinal symptoms were also common with diarrhoea and pain, as well as angiokeratomas and hypohidrosis (inadequate sweating). The Committee noted that hyperhidrosis was uncommonly observed, and typically presented in 11.9% females and 6.4% males (Mehta et al, QJM. 2010;103:641-59). The Committee members were made aware of other symptoms involved the eyes with 73% of males and 77% of females affected by vortex keratopathy 'cornea verticillata', as well as conjunctival and retinal vasculopathy that is known to correlate with disease severity. In addition, 30% of males experience a posterior lens cataract which is referred to as "Fabry" cataract. In addition to the eyes, other sensory organs are also affected with 50-60% experiencing sensorineural hearing loss, as well as tinnitus and vertigo.

6.25. The Committee noted the Bolsolver et al. J Inherit Metab Dis 2014;37:177-87 systematic review, with people with Fabry disease having an increased risk of depression, low mood and fatigue.

6.26. The Committee members were made aware that the main causes of death for those with Fabry disease were cardiac, renal, stroke and suicide. Cardiac symptoms typically commence around 30-40 years of age, with left ventricular hypertrophy, fibrosis, and arrhythmias, with cardiac death the leading cause of death for 34% of males and 57% of females. In the kidneys, proteinuria can lead to renal failure, with a decline in the estimated glomerular filtration rate (eGFR) function. The Committee noted that this was the leading cause of death in 42% (males) of those with Fabry disease prior to enzyme replacement therapy. Cerebrovascular disease accounted for 25% (females) of deaths prior to 2001, and pulmonary features such as chronic bronchitis or a wheeze with obstructive pattern can occur (Mehta et al, J Med Genet 2009;46:548-52).

6.27. The Committee noted the Bolsolver et al. 2014 systematic review's reporting that people with Fabry disease have an increased risk of suicide that is greater than other disorders associated with chronic pain. Overall, the Committee noted that life expectancy of those with Fabry disease is 58.2 in males and 75.4 in females.

6.28. The Committee noted that the current treatment options in New Zealand were monitoring and review of the individual, with treatment to alleviate symptoms, and treat the presentation of the disease. The Committee noted that renal disease is often not diagnosed early, as proteinuria is not significant until rapid reduction in eGFR. The Committee considered the Ng et al. Kidney Int Rep. 2021;6:2481–85 study analysing ANZDATA Australia/New Zealand renal dialysis and transplant registrations, which reported worse morbidity and mortality outcomes from dialysis and kidney transplant in those with Fabry disease.

6.29. The Committee considered evidence from the New Zealand National Metabolic Service Basic Clinical database, which estimated over time it had identified

approximately 65 people with Fabry disease. Of these approximately 10 had died, whilst there were around 55 live individuals, of which 43 were female. The Committee noted that females were overrepresented and were often diagnosed due to their fathers dying of the disease. The Committee noted that less genetic testing occurs in Māori. It may be possible that specific variants are more common in the Māori population and that these may be missed through standard genomic testing, as was the case with the common Taiwanese intronic variant IVS4+919G>A.

6.30. The Committee considered further evidence from the New Zealand National Metabolic Service Basic Clinical database that estimated that currently in Aotearoa New Zealand there were 18 people who had significant disease burden or deteriorating end organ disease who were considered would benefit from treatment. It was estimated that of the total people recorded in the database who have active disease (n=55), 30 have migalastat responsive mutations, with a small number continuing to receive migalastat from the supplier as part of a compassionate access programme from the original migalastat clinical trial (AT1001),who were said to all be receiving good benefit.

6.31. The Committee members were made aware that symptomatic males and females currently had quality of life-limiting pain, gastrointestinal symptoms, and fatigue, as well as some with progressive cardiomyopathy and cardiac conduction defects. The Committee members were made aware that a number of those with symptomatic Fabry disease had mild proteinuria, although none of those people recorded in the New Zealand Metabolic database currently have progressive and severe renal failure, or major issues with cardiac or cerebrovascular disease. There are several individuals who have an unusual phenotype with severe gastrointestinal disease and interstitial lung disease.

6.32. The Committee noted that there was likely to be a higher number of those with Fabry disease in New Zealand than currently seen at the National Metabolic Service, due to lack of diagnosis or genetic testing. The Committee noted Ng et al. 2021's reporting 55 people in ANZDATA having Fabry disease, of 81,890 registrants in Australia and New Zealand receiving renal dialysis and/or renal transplantation from 1965 to 2017. The Committee noted the Chin et al. Lancet Reg Health West Pac. 2022;19:100344 study, which reported the Fabry disease accounted for 34% of all diagnoses of lysosomal storage disorders in Australia for 2009-2020 (258/766 cases), with an incidence of 6.96 per 100,000 and a prevalence of 6.98 per 100,000.

6.33. The Committee noted from Rolfs et al. Lancet. 2005 19;366:1794-6 that of Germans aged 18-55 years in 2001-2004 who experienced stroke of unknown origin, 4.9% of males and 2.4% of females had Fabry disease, being 3.8% overall (28/721), this in turn corresponded to 1.2% in younger adults who suffer any stroke.

6.34. The Committee also noted later evidence from the same lead author (Rolfs et al Stroke. 2013;44:340-9) from 15 European countries in 2007-2010 (median age 46 years), which reported that of 5023 people who were diagnosed with a stroke (comprising ischemic stroke (3396), haemorrhagic stroke (271), transient ischemic attack (1071)), 27 (0.5% (0.4-0.8% CI)) were diagnosed with Fabry disease. Probable Fabry disease was suspected in a further 18 (0.4%).

Health benefit

6.35. The Committee noted that agalsidase alfa is a recombinant enzyme replacement therapy (ERT) that is administered by intravenous infusion once every two weeks. The Committee noted French consensus recommendations for the treatment, and management of Fabry disease (Germain et al. Clin Genet. 2019;96:107-17), where ERT was stated to improve neurological symptoms including neuropathic pain, hearing loss, vestibular function and hypohidrosis. ERT was also stated to potentially

improve white matter lesions, however, did not seem to reduce stroke risk. In the renal system, ERT was said to reverse Gb3 accumulation in podocytes and in the distal tubular epithelium after 11 months of treatment. Complete clearance of Gb3 inclusions was observed in the glomerular endothelial cells and mesangial cells in all treated after 5 years of enzyme replacement therapy. ERT was also stated to stabilise or minimise eGFR decline in those with chronic kidney disease stage 1-3.

6.36. The Committee also considered the Germain et al. Genet Med. 2013;15:958-65 registry-based cohort study, which reported ERT with agalsidase beta was associated with reduced or stabilised left ventricular mass index (LVMI) to -3.6g/year in those treated who were aged 18-29 years compared to an increase of 9.5g/year in those untreated. The study reported an increase in LVMI associated with treatment being started in those older than 40-50 years in the absence of fibrosis.

6.37. The Committee considered the health benefits of agalsidase beta are similar to that of agalsidase alpha.

6.38. The Committee considered the Beck et al. Orphanet J Rare Dis. 2022 20;17:238 review of the Fabry Outcome Survey (FOS) international registry's experience, which reported starting ERT at age ≤ 18 years attenuated the progression of renal disease and cardiomyopathy, whereas those receiving ERT for similar durations who started treatment as adults (> 18 years) had statistically significant worsening in eGFR.

6.39. The Committee noted that clinical trial evidence had been previously reviewed by the Committee and no new clinical trials had been performed. The Committee noted its previous considerations that agalsidase alfa stabilises Fabry preventing further deterioration in people who have not yet developed end stage disease, and that people with Fabry disease who are treated earlier benefit most from treatment.

6.40. The Committee noted that migalastat is a pharmacological chaperone that can be administered to those with specific variants of the GLA protein, and that they had previously reviewed clinical trial data for migalastat in September 2019. The Committee noted it had previously considered the ATTRACT study (Hughes et al. J Med Genet. 2017;54:288-96), which reported migalastat and ERT had comparable effects on renal function over 18 months. The study reported that eGFR -0.3 ml/min/m^2 vs historical untreated male data that showed reductions up to -12.2 ml/min/m^2. Treatment with ERT and migalastat showed similar rates of major clinical events. The study reported a significant reduction in LVMI -6.6 g/m^2 (CI -11.0-2.2) with migalastat but not with ERT.

6.41. The Committee considered the subsequent Feldt-Rasmussen et al, 2020. Mol Genet Metab. 2020;131:219-28 study that reviewed the longer-term efficacy and safety of migalastat in the ATTRACT study (18 months duration), with results from the 12-month open label extension. The study consisted of 52 people, n=31 in Group one who had received migalastat for the whole trial period, and n=15 in Group 2 who had crossed over from ERT to migalastat for the open label extension. The study reported that in Group 1 individuals there was an increased mean annualised rate of change from baseline to month 30 compared to group 2 ERT period and open label extension period (−1.7 mL/min/1.73 m^2, −2.0 mL/min/1.73 m^2 −2.1 mL/min/1.73 m^2 respectively). There was no significant change from baseline in 24-hour urine protein was observed in any group. When considering LVMI, Group 1 was stable from baseline to month 30 (mean change: −3.8 g/m2) but significantly decreased in people with left ventricular hypertrophy at baseline (n = 10; mean change: −10.0 g/m^2. Group 2 during open label extension period, mean LVMI remained unchanged (−0.3 g/m^2). Similarly, mean LVMI in people with left ventricular hypertrophy remained stable (−3.7 g/m^2). There was no change in other cardiac measurements. In Group 1, 10/31 (32.3%) people had renal or cardiac events (35 events total) during the 30-month study. During open label extension, 29.0% (9/31) had renal events but no cardiac

events; 3 people experienced a new event relative to the initial study. In Group 2 when receiving ERT, 6/15 (40.0%) had a renal, cardiac, or cerebrovascular event (17 events total). During the open label extension period 6/15 (40.0%) experienced a composite clinical outcome (27 events total). 5 individuals had renal events and 1 person had both renal and cardiac events. 3 people had new events relative to the initial study period: 2 renal events and 1 cardiac event. The mean time to first occurrence was 246.9 days.

6.42. The Committee further considered the Hughes et al. Am J Med Genet A. 2019;179:1069-73 research letter describing observed safety outcomes with switching to migalastat from ERT in the ATTRACT study. The most common migalastat treatment adverse events in the 18-month randomised clinical trial portion of ATTRACT were nasopharyngitis (33%) and headache (25%). The most common adverse events in the following open label extension (12 months) were: nasopharyngitis (42%), headache (36%), and influenza (27%). Adverse events were generally mild or moderate and no individual discontinued due to an adverse event. Most common adverse events in the cross over group during their 12 months of migalastat treatment (following their ERT treatment during the earlier randomised portion of the trial) included nasopharyngitis (33%), diarrhoea (27%), vomiting (27%), influenza (20%), and headache (20%). Migalastat was generally well tolerated, and no participants discontinued treatment due to adverse events.

6.43. The Committee considered the Narita et al. Clin Exp Nephrol. 2020;24:157-66 study that reviewed the adverse events from the ATTRACT study in a Japanese sub-population. A total of 7 people were included, with 5 treated with migalastat, and a further 2 with ERT. Those on migalastat treatment experienced increased leukocyte alpha-galactosidase A activity, stabilised renal function with mean annualised rate of change in $eGFR_{CKD\text{-}EPI}$ baseline to month 18 was −1.8 mL/min/1.73 m^2 for the migalastat group (n = 5) and 1.6 mL/min/1.73 m^2 for the ERT group (n = 1) Decreased LVMI at 18 months in the migalastat group mean change was −13.8 g/m^2. The change in the Japanese population was greater than overall ATTRACT patient population (−13.8 g/m^2 vs −6.6 g/m^2). Those who had baseline left ventricular hypertrophy had greater decrease of LVMI (−19.4 g/m^2) in migalastat group (n = 5), which persisted to month 30. Plasma lyso-Gb3 levels remained low and stable through to 30 months. The mean change to 18 months was 0.06 nmol/L whilst mean change 30 months was −0.04 nmol/L (95% CI −1.80 to 1.70). The long-term extension study reported that efficacy of migalastat was maintained for up to 48 months. When reviewing safety there was a renal event in 1/5 in the migalastat group during the 18-month study and a cardiac event in 1/2 in the ERT group. The frequency of adverse events from baseline to month 30 was 100% in the migalastat group (5 of 5 people). All adverse events were mild or moderate.

6.44. The Committee also considered the Germain et al. Genet Med. 2019;21:1987-97 phenotypic cohort study stratifying outcomes in the Phase 3 randomised, multicentre, double-blind placebo-controlled FACETS clinical trial of migalastat (6 months) and its open-label extension study (12 months) according to two migalastat-amenable GLA variants, ie in those treated with migalastat with classic Fabry disease phenotype (n = 14; males with residual peripheral blood mononuclear cell α-galactosidase A <3% normal and multiorgan system involvement) compared with other participants (n = 36; males not meeting classic phenotype criteria and all females).

6.44.1. The study reported an increase in α-Gal A activity in vitro, as well as an increase in mean annualised rate of change in $eGFR_{CKD\text{-}EPI}$ to month 24 was −0.3 (3.76) mL/min/1.73 m^2 (95% CI: −2.80, 2.25; n = 11) and −0.3 (4.47) mL/min/1.73 m^2 (95% CI: −2.0, 1.4; n = 30) in classic and other phenotypes respectively. Mean change from baseline to month 24 in LVMI was −16.7 (18.64) g/m^2 (95% CI:

−31.1, −2.4; n = 9) in those with the classic phenotype Fabry disease and −3.2 (18.66) g/m^2 (95% CI: −12.5, 6.1; n = 18) in other forms of Fabry disease.

6.44.2. The study also reported that following 6 months of treatment with migalastat, those with the classic phenotype had improved scores in Gastrointestinal Symptoms Rating Scale diarrhoea subscale (GSRS-D) (mean change from −0.3 [0.77]; 95% CI: –1.0, 0.4; n = 7) whilst placebo had a small increase (0.2 [0.46]; 95% CI: –0.2, 0.7; n = 7). Mean change from baseline in diarrhoea symptoms was −0.9 (1.66; n = 10) in those with the classic phenotype and −0.5 (1.01; n = 31) in those with other phenotypes at 24 months. 88% with classic phenotype who had diarrhoea symptoms at baseline achieved a minimal clinically important differences reduction of 0.33 in GSRS-D.

6.45. The Committee considered there was insufficient evidence at present to evaluate the health benefit of concomitant agalsidase alfa and migalastat treatment.

6.46. The Committee considered that those people with early end organ disease could benefit the most from the funding of agalsidase alfa and migalastat.

Suitability

6.47. The Committee noted that agalsidase alfa is a recombinant ERT, that is administered by intravenous infusion, once every two weeks. The Committee noted that in home infusions would reduce the burden on the individual and their whānau.

6.48. The Committee noted that migalastat is an oral treatment, administered on alternative days, reducing the burden on the individual to attend an infusion service. The Committee noted that migalastat is currently under evaluation with Medsafe, and not currently registered.

Cost and savings

6.49. The Committee noted that intravenous infusion will incur costs in the form of increased health sector resource use, such as additional nurse, clinician, and infusion services. There will also be a small cost associated with compounding, which may require additional nurse time or a payment to external providers, as well as increased monitoring.

6.50. The Committee noted that there would be health care savings including for renal dialysis and cardiac procedures, as well as savings for the individual being treated and improve their ability to undertake daily activities and reduce the potential burden of care for their whānau.

6.51. The Committee noted that other countries had set up home infusions, which could limit time spent in an outpatient setting for the individual treated, as well as reduce pressure on infusions services within clinics. The Committee noted that several suppliers provide ‘at home’ infusion services funding. The Committee noted that home infusions are already occurring successfully for other forms of ERT in Aotearoa New Zealand.

6.52. The Committee noted that genotyping and phenotyping of those with Fabry disease should be undertaken before initiating treatment. The Committee noted that it expected approximately 50% of those with Fabry disease would receive agalsidase alfa, and 50% migalastat, with those with the amenable mutations receiving migalastat as a first line treatment. The Committee considered that it may be appropriate for those with Fabry to transition from migalastat to ERT.

6.53. The Committee noted that quality of life of those treated would also improve through a reduction in symptoms. The Committee also noted that Fabry disease affects renal, cardiac, vascular, and gastrointestinal systems as well as resulting in uncontrolled chronic pain. The Committee noted that some of those with Fabry disease present

with atypical manifestations, and considered Special Authority criteria should reflect this.

Funding criteria

6.54. The Committee noted that cardiac experts for Fabry disease in New Zealand could review the cardiac specific Special Authority criteria to ensure they are disease specific and appropriate for the New Zealand population with Fabry disease.

6.55. The Committee noted that the chronic pain Special Authority criteria should be reviewed to ensure they are disease specific and appropriate for the New Zealand population with Fabry disease.

6.56. The Committee reiterated its view that Special Authority criteria should reflect Fabry disease presenting at times with atypical manifestations.

Summary for assessment

6.57. The Advisory Committee considered that the below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for agalsidase alfa and migalastat if it were to be funded in New Zealand for Fabry disease. This PICO captures key clinical aspects of the proposal and may be used to frame any future economic assessment by Pharmac staff. This PICO is based on the Advisory Committee's assessment at this time and may differ from that requested by the applicant. The PICO may change based on new information, additional clinical advice, or further analysis by Pharmac staff.

Population	People with Fabry disease who have at least one of the following complications: • Renal disease • Cardiac disease • Ischaemic vascular disease • Fabry-related gastrointestinal issues • Other manifestation with significant HRQoL impacts as determined by relevant specialist
Intervention	Agalsidase alfa 0.2mg/kg body weight every two weeks via 40-minute intravenous infusion
Comparator(s) (NZ context)	Best supportive care and treatment of symptoms
Outcome(s)	• Slower decline in renal function • Slowed progression of cardiac disease • Reduced risk of stroke • Longer survival • Improved HRQoL

Table definitions:

Population: The target population for the pharmaceutical, including any population defining characteristics (eg line of therapy, disease subgroup)

Intervention: Details of the intervention pharmaceutical (dose, frequency, treatment duration/conditions for treatment cessation).

Comparator: Details the therapy(s) that the patient population would receive currently (status quo – including best supportive care; dose, frequency, treatment duration/conditions for treatment cessation).

Outcomes: Details the key therapeutic outcome(s), including therapeutic intent, outcome definitions, timeframes to achieve outcome(s), and source of outcome data.

Population	People with Fabry disease *with an amenable GLA mutation as determined by genotypic testing* who have at least one of the following complications: • Renal disease • Cardiac disease • Ischaemic vascular disease • Fabry-related gastrointestinal issues • Other manifestation with significant HRQoL impacts as determined by relevant specialist
Intervention	Migalastat hydrochloride 150 mg every other day via oral tablet.
Comparator(s) (NZ context)	Best supportive care and treatment of symptoms
Outcome(s)	• Slower decline in renal function • Slowed progression of cardiac disease • Reduced risk of stroke. • Longer survival • Improved HRQoL
Table definitions: **P**opulation: The target population for the pharmaceutical, including any population defining characteristics (eg line of therapy, disease subgroup) **I**ntervention: Details of the intervention pharmaceutical (dose, frequency, treatment duration/conditions for treatment cessation). **C**omparator: Details the therapy(s) that the patient population would receive currently (status quo – including best supportive care; dose, frequency, treatment duration/conditions for treatment cessation). **O**utcomes: Details the key therapeutic outcome(s), including therapeutic intent, outcome definitions, timeframes to achieve outcome(s), and source of outcome data.	

7. Teduglutide for the treatment of short bowel syndrome with type III intestinal failure

Application

7.1. Advisory Committee reviewed updated information from the supplier for the use of teduglutide (Revestive) for the treatment of short bowel syndrome with type III intestinal failure (SBS-IF), originally reviewed by the Rare Disorders Subcommittee in 2018.

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

Recommendation

7.3. The Advisory Committee **recommended** that teduglutide be listed with a **high priority** for the treatment of children with short bowel syndrome and intestinal failure within the context of treatment of gastrointestinal disease subject to the following Special Authority criteria:

> **Initial application** – only from a relevant specialist. Approvals valid for 6 months for applications meeting the following criteria:
> All of the following:
> 1. Patient has short bowel syndrome; and
> 2. Patient is 18 years of age or under; and
> 3. Patient has a history of needing parenteral support for at least 3 months; and
> 4. Patient requires at least three days a week of parenteral support; and
> 5. The patient must be stable on their parenteral support regimen for at least four consecutive weeks before initiating teduglutide treatment; and

Renewal – only from a relevant specialist. Approvals valid for 12 months for applications meeting the following criteria:

1. Patient continues to benefit from treatment; and
2. Patient has a quantitative reduction in parenteral nutrition caloric requirements from baseline by week 26 of treatment; and a 25% reduction of PN caloric requirements from baseline by week 52 of treatment

7.4. The Advisory Committee **recommended** teduglutide be listed with a **medium priority** for the treatment of adults with short bowel syndrome and intestinal failure within the context of treatment of gastrointestinal disease subject to the following Special Authority criteria:

Initial application – only from a relevant specialist. Approvals valid for 12 months for applications meeting the following criteria:
All of the following:

1. Patient has short bowel syndrome with Type III intestinal failure due to major intestinal resection; and
2. Patient is over the age of 18; and
3. Patient has a history of dependence on parenteral support for at least 12 months; and
4. Patient requires at least three days a week of parenteral support; and
5. The patient must be stable on their parenteral support regimen for at least four consecutive weeks before initiating teduglutide treatment; and

Renewal – only from a relevant specialist. Approvals valid for 12 months for applications meeting the following criteria:

1. Patient continues to benefit from treatment; and
2. Patient has a quantitative reduction in parenteral nutrition caloric requirements from baseline by week 26 of treatment; and a 25% reduction of PN caloric requirements from baseline by week 52 of treatment

7.5. In making these recommendations, the Advisory Committee considered:

- the high health needs of individuals with SBS-IF reliant on parenteral nutrition, and the high health needs of their whānau
- the evidence from trial data demonstrating long term efficacy and safety of teduglutide in both adults and children
- the potential to achieve enteral autonomy from parenteral feeding when treated with teduglutide, particularly for children with SBS-IF
- the high cost and poor incremental cost effectiveness of teduglutide in adults with SBS-IF
- the potential for high wastage of teduglutide, especially when used in children.

Discussion

Māori impact

7.6. The Committee discussed the impact of funding teduglutide for the treatment of short bowel syndrome with intestinal failure (SBS-IF) on Māori health areas of focus and Māori health outcomes. The Committee noted an abstract of a study detailing information on children with intestinal failure using data from the New Zealand National Intestinal Failure Service registry (Andrews et al. Transplantation.2019;103(7S2):S42). The Committee noted that the abstract reported that Māori children were marginally overrepresented accounting for 28% of the population cohort respectively, compared to 26% of the New Zealand paediatric population.

Background

7.7. The Committee noted that it reviewed an application for teduglutide for SBS-IF in November 2018 where it recommended that the application be declined, based on

the modest evidence of short-term benefit provided by treatment, lack of long-term data, and safety concerns. The Committee noted that PTAC reviewed the record from the Subcommittee meeting in February 2019, where it accepted the Subcommittee recommendation that the application be declined.

7.8. The Committee noted that, in 2021, additional correspondence was received from the supplier providing further information for consideration and outlining the need for teduglutide for individuals with SBS-IF. The Committee noted that additional applications had also been received from Te Whatu Ora (endorsed by the New Zealand National Intestinal Failure & Rehabilitation Service) regarding evidence for the use of teduglutide in children. The Committee also noted that Pharmac had received additional supporting evidence from NPPA applications.

7.9. The Committee noted that, at the time of the November 2018 meeting, teduglutide was not approved by Medsafe, but has been subsequently approved for use in adults.

Health need

7.10. The Committee noted that SBS-IF can result from a variety of underlying causes (such as injury, vascular disease, cancer, resection, Crohn's disease) which leads to a highly heterogenous population of individuals with SBS-IF with differing residual bowel anatomy, comorbidities, and clinical management requirements.

7.11. The Committee noted that SBS-IF results from a drastically reduced length of small intestine (to <200cm) and that individuals with SBS-IF experience a range of symptoms including diarrhoea, nutrient deficiencies, weight loss, electrolyte disturbances, dehydration, and malnutrition. The Committee noted that individuals with SBS-IF are reliant on ongoing parenteral support for survival with the requirement to be hooked-up via intravenous line to an infusion pump for an average of 12 hour per day, five times per week. The Committee noted that this has substantial quality of life impacts for individuals with SBS-IF in relation to their sleep, and ability to work and socialise.

7.12. The Committee noted that, with current standard of care, only half of individuals on parenteral support survive more than ten years due to the development of life-threatening complications (such as sepsis, blood clots, or liver damage) associated with parenteral support and intravenous feeding.

7.13. The Committee noted that whānau and caregivers of individuals with SBS-IF also face substantial quality of life impacts as they need to devote physical, emotional and financial resources to caring for their family member with SBS-IF. The Committee noted that whānau often have to take time off work or other obligations in order to offer care, assist with preparing and administering intravenous feeding, assisting with physical hygiene, and transport to medical appointments. The Committee noted that whānau of individuals receiving parenteral support report a lack of social activities, disrupted familial and other relationships, lost friendships, withdrawal of external support, and repeated episodes of depression.

7.14. The Committee noted an abstract of a study detailing information on children with intestinal failure using data from the New Zealand National Intestinal Failure Service registry (Andrews et al. Transplantation.2019;103(7S2):S42). The Committee noted that the abstract reported that 56% of the group reported were male, 44% had been born preterm, and that Pacific and Māori children were marginally overrepresented accounting for 13% and 28% of the population cohort respectively, compared to 9% and 26% of the New Zealand paediatric population.

7.14.1. The Committee also noted that people with IF living in areas of high New Zealand socioeconomic deprivation were overrepresented, with 36% in the highest deprivation quintile and 9% in the least deprived quintile, compared to

24% and 19% respectively of the New Zealand paediatric population. The Committee noted that, in the abstract, SBS caused IF in 18% of cases, although for preterm neonates the prevalence of short bowel syndrome was higher (36%).

Health benefit

7.15. The Committee noted the following recommendations from other jurisdictions regarding the use of teduglutide in the treatment of SBS-IF:

7.15.1. The PBAC (Australia) recommended that teduglutide be funded for adults with SBS-IF in 2019, noting the high clinical need and the possibility that teduglutide may reduce the burden associated with parenteral support. The PBAC then recommended that teduglutide be funded for children with SBS-IF in 2021 noting that the restriction should not specify any age criteria given teduglutide has been studied in paediatric individuals and was shown to be well tolerated. The PBAC noted that input from a paediatric advisory board formed the basis of, and justification for the submission's request to include a 20% reduction in weekly parenteral support volume as a response criterion for paediatric individuals.

7.15.2. The CDEC (Canada) recommended in 2016 that teduglutide be funded for adults with SBS-IF, and extended its recommendation to include children (2019) aged one year and above who are dependent on parenteral support.

7.15.3. The SMC (Scotland) recommended teduglutide for restricted use in NHS Scotland for individuals one to 17 years with SBS in 2018, and extended this recommendation to include funding for adults in 2020.

7.15.4. NICE (Wales/UK) recommended funding of teduglutide as an option for treating short bowel syndrome (SBS) in people 1 year and above in 2022. NICE noted that clinical trial evidence showed that teduglutide reduces the number of days a week people with SBS require parenteral support compared with placebo, however, how much it reduces this is uncertain because the trial design may not reflect clinical practice.

7.16. The Committee noted that the primary evidence available at the time of the November 2018 assessment of teduglutide for SBS-IF came from the STEPS randomised phase III clinical trial of teduglutide versus placebo in adults with SBS-IF with dependency on parenteral support at least three times per week (Jeppesen et al. Gastroenterology. 2012;143:1473-1481). The Committee noted that, in this trial, teduglutide offered at 33% improvement in response (measured as ≥20% reduction in parenteral support requirement) over placebo. The Committee noted that 54% of participants in the teduglutide treatment arm had a ≥1 day reduction in weekly parenteral nutrition requirements versus 23% with placebo. The Committee noted that there was minimal difference in treatment emergent adverse events between treatment arms, and that the most common treatment emergent adverse events in the teduglutide treatment arm were abdominal pain, nausea, gastrointestinal stoma complications, and abdominal distension.

7.17. The Committee noted that in the STEPS quality of life analysis (Jeppesen et al. Clin Nutr. 2013;32:713-21), parenteral support reduction was associated with statistically significant quality of life improvements compared to baseline, which were not seen in those treated with placebo. However, the Committee noted additional cohort studies and randomised controlled trials (listed below) that indicated no impact of teduglutide on quality of life and so it was unclear from the published evidence if there was a meaningful quality of life improvement, particularly for a one-day reduced requirement for parenteral support. The Committee considered that one day less of parenteral support would not reduce the risks associated with intravenous feeding.

7.18. The Committee also noted the STEPS-2 2-year open-label extension of the STEPS trial (Schwartz et al. Clin Transl Gastroenterol. 2016;7:e142) signalling that positive results with teduglutide persisted.

7.19. The Committee also noted Study 004 (Jeppesen et al. Gut. 2011;60:902-14) and Study 005 (O'Keefe et al. Clin Gastroneterol Hepatol. 2013;11:815-23) investigating the effects of teduglutide at a dose of 0.10mg/kg and 0.05mg/kg compared to placebo in adults with SBS-IF needing parenteral support. The Committee noted that superiority of one dose of teduglutide over the other was not demonstrated. The Committee noted that nausea was an adverse event commonly associated with teduglutide.

7.20. The Committee noted an additional trial published since its previous consideration of teduglutide, Kocoshis et al. JPEN J Parenter Enteral Nutr. 2020;44:621-31:

7.20.1. This was a phase III trial with 2 randomised, double-blind teduglutide dose groups and a nonblinded standard of care (SOC) arm investigating the safety and efficacy teduglutide in paediatric patients with SBS-IF. Participants received 0.025 mg/kg (n=24) or 0.05 mg/kg (n=25) teduglutide once daily or SOC alone (n=9).

7.20.2. The primary end point (≥20% reduction in parenteral support) was achieved by 13 (54.2%) in 0.025mg/kg/day arm, 18 (69.2%) in the tedulgutide 0.05 mg/kg/day arm, 18 (69.2%) in the 0.05 mg/kg/day arm, and 1 (11.1%) in the SOC arm (p <0.05 vs. SOC). Both 0.025mg/kg and 0.05mg/kg teduglutide treated groups showed clinically significant reductions in parenteral support volume (P < 0.05 vs SOC), parenteral support calories, days per week and hours per day of parenteral support infusions and increases in enteral nutrition and plasma citrulline at week 24 compared with baseline.

7.20.3. Two (8.3%, 0.025 mg/kg teduglutide) and three individuals (11.5%, 0.05 mg/kg teduglutide) achieved enteral autonomy. The most common treatment related adverse events were pyrexia and vomiting.

7.21. The Committee also noted a number of observational studies relating to the use of teduglutide in the treatment of SBS-IF:

- Martin et al. Am J Clin Nutr. 2021;113:1343-50
- Allard et al. J Paranter Enteral Nutr. 2021;45 (S1):P25
- Puello et al. JPEN J Parenter Enteral Nutr. 2021;45:318-22
- Penvy et al. Clin Nutr ESPEN. 2020;40:436-7
- Joly et al. Clin Nutr. 2020;39:2856-62
- Robles et al. Eur J Clin Pharm. 2020;3:166-70 (Abstract only)
- Chiplunker et al. Gastroenterology. 2020;158:Supplement S37
- Solar et al. JPEN J Parenter Enteral Nutr. 2021;45:1072-82
- Chen et al. Unit Eur Gastroenterol J. 2019;7(S7.8):1012-4
- He et al. J Gastroen Hepatol. 2019;34(S2):194-5
- Regano et al. Nutrition. 2019;65(S):5
- Abdullah et al. Gastroenterology. 2019;156(S1):S62
- Ukleja et al. JPEN J Parenter Enteral Nutr. 2018;42:821-25
- Ring et al. Expert Rev Gastroenterol Hepatol. 2018;12:257-64

- Lam et al. JPEN J Parenter Enteral Nutr. 2018;42:225-30
- Schoeler et al. Therap Adv.Gastroenterol. 2018;11:1756284818793343
- Lambe et al. Transplantation. 2021;105(7S):O-03
- Wong et al. J Pediatr Surg. 2022;57:143-8
- Belza et al. JPEN J Parenter Enteral Nutr. 2022;online ahead of print
- Teran et al. Transplantation. 2021;105(7S):S59
- Kinberg et al. Transplantation. 2021;105(S7):S67
- Boluda et al. J Pediatr Gastroenterol Nutr. 2020;71:734-9
- Hill S. J Pediatr Gastroenterol Nutr. 2020;71:697-8
- Bioletto et al. Nutrients. 2022;14:796
- Falco et al. Front Nutr. 2022;9:866048
- Chen et al. Clin Nutr ESPEN. 2021;43:420-7
- Chen et al. JPEN J Parenter Enteral Nutr. 2020;44:119-28
- Seidner et al. Nutr Clin Pract. 2018;33:520-7
- Gigola et al. Front Nutr. 2022;9:866518

7.22. The Committee noted that the studies ranged widely in quality and numbers of participants and considered that the data was highly heterogenous. The Committee noted that overall, teduglutide reduced the number of days of parenteral nutrition (and sometimes led to complete discontinuation of parenteral nutrition), and that ≥20% reduction in parenteral nutrition varied from 60-100% in the studies presented. The Committee also noted that abdominal pain, pyrexia and nausea were the most common adverse events relating to teduglutide, that stoma enlargement was often reported, that longer exposure on teduglutide resulted in a higher proportion of participants meeting study endpoints over 6 to 12 months of 40% to 70%, and that colorectal cancer was not increased with use of teduglutide but that the incidence of colon polyps increased.

7.23. The Committee noted that post hoc analysis of the STEPS and STEPS-2 trials by Chen et al. reported that having a stoma was a predictor of positive response, and that predictors of negative response were vascular disease, ileocecal valve presence, and being of female gender. The Committee also noted that those with inflammatory bowel disease, stoma, and without colon in continuity had a shorter time to response. The Committee considered that a reduction in parenteral nutrition has downstream intestinotrophic benefits and may reduce the risk of sepsis.

7.24. The Committee considered that the strength and quality of evidence for the use of teduglutide in the treatment of SBS-IF was moderate.

Suitability

7.25. The Committee considered that individuals with SBS-IF are unlikely to have concerns regarding daily subcutaneous injection with teduglutide or frequent monitoring visits as these individuals are actively involved in their own treatment, well acquainted with the health system, and can often administer their own parenteral support from home.

Cost and saving

7.26. The Committee noted that, although there is evidence that teduglutide may reduce the need for parenteral support, it would likely not eliminate the need for parenteral support in most patients. The Committee noted that the cost of teduglutide would be

in addition to the cost of current treatment for the majority of individuals with SBS-IF. The Committee also considered that improvements in quality of life associated with teduglutide in the requested population are likely to be gained but noted that there is limited evidence of this in the currently published literature.

7.27. The Committee noted that one 5mg vial of teduglutide is adequate for an individual weighing up to 100kg and that the dose should be determined based on the weight of the individual receiving treatment. The Committee noted that the vial is for single use in one individual only and that any residue should be discarded, which would lead to substantial wastage of product, particularly in the paediatric setting.

7.28. The Committee considered that the number of individuals who would access teduglutide under the suggested criteria is unknown but considered, based on the number of people accessing parenteral nutrition in New Zealand, that numbers are likely to be higher than proposed by the supplier in their 2018 submission. The Committee also considered that it was not clear if SBS-IF met the principles for a rare disorder.

Funding criteria

7.29. The Committee considered that the treatment of children with SBS-IF should be considered differently from the treatment of adults, and children are still growing and accommodating and do not have a static condition. The Committee considered that neonatal cases of SBS-IF where there was more than 25cm of small bowel remaining may be able to eventually achieve autonomy from parenteral feeding. The Committee considered that this scenario would be where treatment with teduglutide would have the most benefit in the reduction of long-term morbidities in these individuals. The Committee considered that those most at risk of intestinal failure and life-threatening complications in the paediatric population were pre-term babies, and those with growth restriction or complicated gastroschisis, all of which are more common in those with lower social determinants of health. The Committee noted again that there is some evidence for enteral autonomy in this population when treated with teduglutide, but that the evidence is not strong.

Summary for assessment

7.30. The Advisory Committee considered that the table below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for teduglutide if it were to be funded in New Zealand for SBS-IF. This PICO captures key clinical aspects of the proposal and may be used to frame any future economic assessment by Pharmac staff. This PICO is based on the Advisory Committee's assessment at this time and may differ from that requested by the applicant. The PICO may change based on new information, additional clinical advice, or further analysis by Pharmac staff.

	Children	Adults
Population	Children with type III intestinal failure and a history of parenteral support for at least 3 months.	Adults with type III intestinal failure due to major intestinal resection and a history of needing parenteral support for at least 12 months. Individuals eligible for teduglutide must be stable on parenteral support for at least four consecutive weeks prior to initiation and have no active gastrointestinal malignancy or history of gastrointestinal malignancy within the last five years.
Intervention	Teduglutide given daily at a dose of 0.05 mg/kg body weight. Patients assumed to not exceed a weight of 100kg and a dose of 5mg daily, plus standard of care.	
Comparator(s)	Standard of care (including enteral feeding, parenteral support, dietary interventions, oral rehydration solutions, and anti-diarrhoeal and anti-secretory agents)	
Outcome(s)	• Treatment response: ○ ≥20% reduction in parenteral support volume from baseline, or ○ reduction in parenteral support frequency of at least one day per week from baseline. • Patient autonomy from parenteral nutrition • Uncertain improvements in health-related quality of life • Nominal health sector savings from reduced parenteral nutrition	
Table definitions: Population, the target population for the pharmaceutical; Intervention, details of the intervention pharmaceutical; Comparator, details the therapy(s) that the patient population would receive currently (status quo – including best supportive care); Outcomes, details the key therapeutic outcome(s) and source of outcome data.		

8. SMA treatments (nusinersen and risdiplam) for the treatment of spinal muscular atrophy (SMA) not funded by the existing funding criteria

Application

8.1. Following feedback on the consultations for the funding of nusinersen and risdiplam, the Advisory Committees reviewed applications for these SMA treatments for the treatment of spinal muscular atrophy (SMA) in people not funded by the existing funding criteria, namely:

- people with SMA types IIIb, IIIc and undefined III aged 18 years and under (symptomatic after 3 years of age)
- people with SMA type II and III who are aged 19 years and over
- people with SMA type IV (aged 19 years and over at symptom onset).

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

Recommendation

8.3. The Advisory Committees **recommended** that the funded access to nusinersen and/or risdiplam be widened to include SMA types IIIb, IIIc and undefined type III within the context of treatments for rare disorders and for neurological disorders with a **high priority** subject to the following Special Authority criteria (changes marked from current funded criteria):

Initial application from any relevant practitioner. Approvals valid for 12 months for applications meeting the following:
All of the following:

1 Person has genetic documentation of a homozygous *SMN1* gene deletion, homozygous *SMN1* point mutation, or compound heterozygous mutation; and
2 Person is 18 years of age or under; and
3 Either
  3.1 Person has experienced the defined signs and symptoms of SMA type I, II or III~~a prior to three years of age~~; or
  3.2 Both:
    3.2.1 Person is pre-symptomatic; and
    3.2.2 Person has three or less copies of SMN2.

Renewal from any relevant practitioner. Renewals valid for 12 months. All of the following:

1 There has been demonstrated maintenance of motor milestone function since treatment initiation; and
2 Person does not require invasive permanent ventilation (at least 16 hours per day), in the absence of a potentially reversible cause while being treated with nusinersen; and
3 ~~Nusinersen n~~**N**~~n~~ot to be administered in combination with other SMA disease modifying treatments or gene therapy.

8.4. In making this recommendation the Committees considered:

- The high unmet health need of people with SMA type III;
- The overlap in health need between people with SMA type IIIa and types IIIb and IIIc;
- While the SUNFISH trial did not include stratified results for type IIIb and IIIc individuals, there was sufficient evidence to show that there was treatment benefit for adults with SMA types II and III in the form of maintaining physical function

8.5. The Advisory Committees **recommended** that the funded access to nusinersen and/or risdiplam be widened to include SMA types II and III where individuals initiate treatment at age 19 years or older, within the context of treatments for rare disorders and neurological disorders with a **high priority** subject to the following Special Authority criteria (changes marked from current funded criteria):

Initial application from any relevant practitioner. Approvals valid for 12 months for applications meeting the following:

1 Person has genetic documentation of a homozygous *SMN1* gene deletion, homozygous *SMN1* point mutation, or compound heterozygous mutation; and
~~2 Person is 18 years of age or under; and~~
3 Either
  3.1 Person has experienced the defined signs and symptoms of SMA type I, II **III** ~~IIIa prior to three years of age~~; or
  3.2 Both:
    3.2.1. Person is pre-symptomatic; and
    3.2.2. Person has three or less copies of SMN2

Renewal from any relevant practitioner. Renewals valid for 12 months.
All of the following:

1 There has been demonstrated maintenance of motor milestone function since treatment initiation; and
2 Person does not require invasive permanent ventilation (at least 16 hours per day), in the absence of a potentially reversible cause while being treated with nusinersen; and
3 ~~Nusinersen n~~**N**ot to be administered in combination with other SMA disease modifying treatments or gene therapy

8.6. In making this recommendation the Committees considered:

- The high unmet health need of adults with SMA types II and III
- The moderate quality of evidence demonstrating clinically important outcomes

8.7. The Advisory Committees **recommended** that the application for nusinersen and risdiplam for the treatment of symptomatic SMA type IV (adult-onset) be **declined**, within the context of treatments for rare disorders and neurological disorders. In making this recommendation the Committees considered:

- That people with SMA type IV have a low health need overall all and significantly lower health need than individuals with SMA types I II and III.
- There was currently no evidence to support the use of SMA treatments in individuals with SMA type IV.

Discussion

Patient lived experience

8.8. A New Zealander with SMA who had recently moved to Australia to access funded treatment and a clinician treating SMA with nusinersen and risdiplam in Australia shared their experiences with the Rare Disorders Advisory Committee, Neurological Committee observers and Pharmac staff. The Committees and Pharmac staff valued this opportunity and considered that it helped to frame the Committees' discussions about treatment of SMA in adults with a different perspective.

8.9. The person with SMA described the losses experienced due to SMA as a cumulative trauma that is constantly affecting their life. They recounted the difficult decision to move from New Zealand in order to access funded treatment, and how their family had to sacrifice being near their support network for this purpose.

8.10. The person described how commencing treatment with nusinersen as an adult had positively impacted their life. They recounted that since receiving treatment they were able to stand stronger, walk further and complete tasks that they had previously lost the ability to do due to SMA symptoms. They described how treatment offered a better life for them, their family, and the economy as they had increased ability to work.

8.11. The clinician treating SMA in adults described how they had observed stabilisation or improvements of SMA symptoms in almost all people they had treated with nusinersen or risdiplam. They recounted that the people they treated shared treatment expectations of stabilisation and maintaining independence, with anything more being experienced as a bonus.

8.12. Both the individual with SMA, and the clinician emphasised that the benefits of treatment with nusinersen or risdiplam should not be underestimated, as even small benefits could make significant differences to people's lives.

Māori impact

8.13. The Committees discussed the impact of funding nusinersen and risdiplam for SMA groups currently under consideration on Māori health areas of focus and Māori health outcomes. The Committees noted unpublished 2023 reporting by Richard Roxburgh and colleagues of the prevalence of SMA in Māori people being approximately 0.34/100,000 live births and corresponding incidence 1.7/100,000 live births (95% CI 0 to 9.3).

8.14. The Committees noted that SMA is not included as a Māori health area of focus in Te Pātaka Whaioranga - Pharmac's Māori responsiveness strategy.

Background

8.15. The Committees noted that from 1 January 2023, nusinersen has been funded for people aged 18 years and under with pre-symptomatic SMA or symptomatic SMA types I, II or IIIa. The Committees noted that Pharmac has recently consulted on a proposal to fund risdiplam from 1 May 2023 with the same access criteria as nusinersen.

8.16. The Committees noted that substantive feedback was received in response to Pharmac's consultation to fund nusinersen and risdiplam, regarding access criteria. The Committees noted that consultation responses included feedback that treatments should be funded for all people with SMA, including those who start treatment after 18 years of age with the types otherwise eligible within the currently proposed criteria, and for individuals with SMA types IIIb, IIIc and IV.

8.17. The current eligibility criteria reflect the population requested in the funding application, the people identified by our clinical advisors as having the highest unmet health need and the most potential to benefit from treatment and aligns with the clinical trial evidence that was considered by our clinical advisors at the time. More information can be found in the Application Tracker record for nusinersen (for SMA types I II and III and pre-symptomatic SMA).

Health Need

8.18. The Committees noted that the incidence of SMA in New Zealand is approximately 0.8/10,000 live births, equating to approximately 4-5 incident cases of SMA per year as per an unpublished study by Rodrigues et al (2021). The Committees noted that the unpublished publication described the current prevalence of SMA in New Zealand as 1.7/100,000 people, or approximately 80 people in total.

8.19. The Committees noted that the unpublished article by Rodrigues et al which stated that epidemiological studies suggest that 50-60% of incident SMA cases are SMA type 1, however due to the short life expectancy SMA type 1 is less prevalent than other forms.

8.20. The Committees noted that SMA presents as a spectrum disease, and that there can be overlap in symptom severity between types. Members noted that the types of SMA are largely defined by the time of symptom onset, but also that there is an inverse correlation between severity and SMN2 copy number. The Committees noted that treatment in the pre-symptomatic setting is based on SMN2 copy number, as symptoms have not yet developed.

8.21. The Committees noted data from the New Zealand SMA registry reporting that around 40 individuals on the registry were over 18 years of age as of 1 March 2023. The Committees noted that due to the voluntary nature of the registry, all people may not be included.

8.22. The Committees noted that individuals who are pre-symptomatic are unable to be classified as type I, II, III or IV, which are defined based on time of symptom onset; and so are classified by the number of SMN2 copies, due to current evidence indicating that number of SMN2 copies correlating inversely with disease severity.

Type IIIb, III c and undefined III:

8.23. The Committees noted that individuals with SMA type III typically develop the ability to walk without assistance and have an unaffected life expectancy, however the Committees recognised that there are a range of mobility limitations ranging from abnormal gait caused by weakness in their hip and/or thigh muscles to loss of ambulation during adolescence or adulthood. In some patients, there may be considerable burden of disease with reduced employment, higher health needs, and

psychological impacts that may be present for much of the individual's adult life. The Committees considered that the impact of SMA over time for people with SMA type IIIb should not be underestimated, noting that they may lose ambulation and require a wheelchair later in life.

8.24. The Committees considered that all individuals with SMA type III represent a high proportion of the prevalent population (given lower to low survival rates in types I and II). The Committees considered that individuals with type IIIa were less likely to be walking at 10 years of age than those with SMA type IIIb. The Committees considered that individuals with type IIIa may have similar orthopaedic surgery needs to individuals with SMA type II, whereas individuals with type IIIb usually reach normal early developmental milestones.

8.25. The Committees considered that people aged 18 years and under with type IIIb, IIIc and undefined III had a high unmet health need. Members considered that at it can be difficult to differentiate between subtypes IIIa, b and c from due to phenotypic overlap and that this in part is likely explained by commonalities in SMN2 copy numbers.

Adults with type II and III:

8.26. The Committees considered that people aged 19 years and over with SMA Type II and III SMA have high unmet health need. Members noted that adults with SMA, as with children with SMA, can experience substantial morbidity and in some cases early mortality. Members noted the impact of frequent medical appointments, hospital admissions, and reliance on carers. The Committees considered that SMA is a progressive disease, with symptoms gradually worsening over time, including the loss of ambulation.

8.27. The Committees considered the health need of families and whānau of people with SMA is similarly high across subtypes and age. The Committees reiterated the comments from PTAC in August 2018; that there is a high health need for family, whānau, and caregivers of SMA patients, and that some families have left New Zealand to seek treatment internationally, such as moving to Australia to access funded treatment, in some cases leaving behind their families, whānau and support systems. The Committees considered that only those individuals belonging to households with the financial means to relocate can make the choice to move overseas, and that those living in more difficult socioeconomic circumstances would not have this option.

Type IV

8.28. The Committees considered that people with SMA type IV have a low health need compared with those with other SMA types. The Committees considered that the nature of SMA type IV symptoms is poorly defined. The Committees noted reports of individuals in their 20s to 40s being ambulant and requiring no respiratory support and/or maintaining a sedentary occupation (Kolb et al. Neurol Clin 2015; 33:831). The Committees considered that SMA type IV is a slow progressing form of SMA where limb weakness occurs gradually, and often without major motor impairments, respiratory impacts or changes to mortality. The Committees noted that the average age at symptom onset of SMA type IV is also poorly defined and that the subtype is broadly defined by individuals experiencing the onset of symptoms after the age of 18 years. The Committees noted that individuals with SMA type IV have a standard life expectancy.

Health Benefit

Nusinersen

8.29. The Committees noted results from an observational prospective longitudinal follow-up study which aimed to determine changes in motor and respiratory function after treatment with nusinersen in adults with SMA (Duong et al. Neurol Clin Pract. 2021;11(3):e317-e327). The Committees considered that the study's population most closely matched the population of individuals with SMA in New Zealand in regard to ambulation status. The Committees noted that individuals were treated for a mean treatment duration of 12.5 months. The Committees considered that some broad objective measures, including various motor and respiratory measures, reported stability rather than the expected decline, while some results reported a non-significant trend towards improvement. The Committees noted that outcomes were not analysed according to subtype of SMA. The Committees considered limitations of the study included that it was observational, non-randomised and, not blinded (but considered that blinded studies were now unlikely to be conducted), the short follow up period, possible selection bias, and imprecision with wide confidence intervals.

8.30. The Committees noted a prospective three year SMArtCARE Registry-based observational longitudinal follow-up study that assessed improvements in walking distance during nusinersen treatment (Pechmann et al. 2023;10(1):29-40). The Committees noted that the study included adult as well as paediatric participants, all whom were walking independently at the start of the study. The Committees noted the mean age of SMA symptom onset was 11 years, and mean age at the start of treatment was 37 years. The Committees noted that 26% of adult participants experienced clinically meaningful improvement of equal to or more than 30 metres in the 6-minute walk time (6MWT) test at the last available visit (up to 38 months).

8.31. The Committees also noted the following reviews:

- Coratti et al. Orphanet J Rare Dis. 2021;16(1):430
- Gavriilaki et al. Neurotherapeutics. 2022;19(2):464-75
- Rad et al. Muscle Nerve. 2022;65(5):498-507
- Janoudi et ak. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health. 2020.

8.32. Committee noted results from Darras et al. Neurology. 2019;92(21):e2492-e2506, a phase 1b/2a study which followed 28 children with SMA, 18 of whom had type III disease. All motor outcomes improved over the 715 day extension arm of the study.

8.33. The Committees considered that the evidence for nusinersen in the groups under consideration is limited to a small number of studies, but that further high quality evidence is unlikely due to the funding of SMA treatments internationally.

Risdiplam

8.34. The Committees noted that there are currently no published studies evaluating the efficacy and safety of risdiplam specifically in an adult population. However, the SUNFISH trial included individuals with SMA types II and III who were aged 2-25 years (median age 9) old at the time of randomisation (Mercuri et al. Lancet neurol. 2022;21:42-52). The Committees noted that 180 participants were included in the study, 22 of whom were aged 18-25 years at randomisation. The Committees noted that 67% of the study population had scoliosis and 25% had had spinal surgery; thus the Committees considered this group to have severely impacted motor function. The Committees noted that results were not stratified into type IIIa, b, or c.

8.35. The Committees noted that in the 18–25-year age group, there was no significant improvement in motor function measure: -0.65 (-4.03 to 2.74), however a significant improvement in the revised upper limb module was observed: 1.74 (-1.06 to 4.53).

8.36. Members considered that the improvements seen for this group represented clinically meaningful outcomes.

8.37. Members considered that while the SUNFISH trial did not include stratified results for type IIIb and IIIc individuals, SMA is a spectrum of disease and so it is reasonable to extrapolate that these group would also receive benefit from treatment.

8.38. The Committees considered an article describing the Clinical experience through Early Access Medicines Scheme (EAMs) Northern Ireland for risdiplam for the treatment of adults with SMA (McCluskey et al. 2023;67(2):157-71). The study included six participants with a mean age of 33.7 years, none of whom had received prior treatment with onasemnogene (due to age) or nusinersen (due to complex spinal anatomy). There was no change in RULM score or respiratory function. There was an Egan Kallifikation 2 (EK2) Mean change -4.5(95%CI -7.3- -1.7, p=0.009), and a quality-of-life measure (QOLM) Mean change of +10.7(95%CI 1.4-19.5, p=0.027). Patients reported a range of observed benefits including multiple motor improvements. All participants reported an overall improvement in strength, sense of wellbeing, and speech quality.

General

8.39. The Committees considered that where evidence was available for only one treatment (ie. risdiplam or nusinersen) within a patient group, that it was reasonable to assume that both treatments would provide the same or similar level of benefit within that group. The Committees noted that this was due to similar mechanisms of action, biological plausibility, and similar outcomes when studies in other subgroups.

8.40. The Committees noted that after the age of 20 years, most of an individual with SMA's motor neurons may be lost, and thus treatment with nusinersen or risdiplam would not be expected to regain lost function. By contrast, those treated early a greater proportion of motor neurons would be protected, with a resultant greater benefit. Members noted that there was limited available evidence to confirm that loss function cannot be regained with treatment. The Committees considered that for adults with SMA, while the published evidence suggests that treatment would not result in a significant improvement in motor function and other symptoms; the demonstrated maintenance of motor function provides a clinically meaningful outcome, which should not be underestimated.

8.41. The Committees noted there was no published evidence which supported the use of nusinersen or risdiplam in individuals with adult-onset SMA (Type IV).

8.42. Members considered that is the funding criteria relating to SMN2 copies were widened to allow for individuals to access treatment with up to 3 SMN2 copies, then most people who would later develop SMA symptoms would be diagnosed and treated symptomatically, however. Members considered that extension of the criteria to include 4 SMN2 copies may include individuals with milder phenotypes who have a reduced cost-benefit for treatment. Members commented it would be appropriate to have guidelines in place to ensure those who are identified as having 4 copies SMN2 copies through pre-symptomatic screening are monitored more closely for the development of symptoms.

Suitability

8.43. The Committees noted that nusinersen is administered intrathecally by a health care professional. The Committees considered that administration of nusinersen is often complicated in individuals with severe scoliosis. Members considered that adults with

SMA types II and III, particularly those who are non-ambulant may experience significant scoliosis and mobility problems, as well as previous orthopaedic surgery, and therefore those affected may require alternative interventions to administer the treatment (Rad et al. Muscle Nerve. 2022;65(5):498-507). The Committees considered that transport to a clinical setting for tri-annual infusions may be difficult for some due to the individuals' ambulation status and potential distance from treatment centres and socioeconomic status. As such, the Committees considered risdiplam, as an oral treatment, would likely be a more suitable treatment and result in less inequity for non-ambulant adults with SMA.

8.44. The Committee considered that due to the size of the risdiplam bottles, the oral liquid would not last long for adult patients. The Committee noted that a tablet form is currently being developed to overcome this problem.

Cost and saving

8.45. The Committees noted that the administration costs associated with giving nusinersen by lumbar puncture were high in comparison with zero administration costs associated with the orally administered risdiplam.

8.46. The Committees also considered that the benefit that could be obtained in people who were over 18 years of age at the time of treatment initiation was likely lower than that obtained for people starting treatment at the time of symptom onset (and far lower than that for people diagnosed and treated pre-symptomatically). However, the Committees considered the magnitude of treatment benefit highly uncertain in economic terms, and that while people with treatment may experience a less severe disease phenotype, advice from specialists treating people in this group would need to be obtained to ascertain the magnitude of benefit and a means of expressing and quantifying it in economic modelling.

Summary for assessment

8.47. The Advisory Committees considered that the below table summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for nusinersen and risdiplam if they were to be funded in New Zealand for SMA in people who did not meet existing funding criteria. This PICO captures key clinical aspects of the proposal and may be used to frame any future economic assessment by Pharmac staff. This PICO is based on the Advisory Committees' assessment at this time and may differ from that requested by the applicant. The PICO may change based on new information, additional clinical advice, or further analysis by Pharmac staff.

<table>
<tr><td>Population</td><td colspan="2">Three subgroups which are not currently included in the proposed Special Authority criteria for the funding of nusinersen and risdiplam:

1. People with SMA type IV
2. People with SMA types II or IIIa who are >18 years of age at the time of initiation of treatment
3. People with SMA types IIIb, IIIc or undefined type III</td></tr>
<tr><td rowspan="5">Intervention</td><td colspan="2">• Nusinersen 6 times in the first year (4 as loading doses), 3 times in subsequent years, administered via intra-thecal injection</td></tr>
<tr><td colspan="2">• Risdiplam once daily oral dose as determined by age and body weight</td></tr>
<tr><td>Age and body weight</td><td>Recommended daily dose</td></tr>
<tr><td>2 months to < 2 years of age</td><td>0.20 mg/kg</td></tr>
<tr><td>≥ 2 years of age (< 20 kg)</td><td>0.25 mg/kg</td></tr>
<tr><td>≥ 2 years of age (≥ 20 kg)</td><td>5 mg</td></tr>
</table>

Comparator(s) (NZ context)	Best supportive care
Outcome(s)	• Motor function (including, where applicable, age-appropriate motor milestones such as sitting, standing and walking) • Bulbar function (including, for example, swallowing and ability to communicate) • Frequency and duration of hospitalisation • Respiratory function • Complications of spinal muscular atrophy (including, for example, scoliosis and muscle contractures) • Need for non-invasive or invasive ventilation • Stamina and fatigue • Mortality • Adverse effects of treatment • Health-related quality of life
Table definitions: **P**opulation: The target population for the pharmaceutical, including any population defining characteristics (eg line of therapy, disease subgroup) **I**ntervention: Details of the intervention pharmaceutical (dose, frequency, treatment duration/conditions for treatment cessation). **C**omparator: Details the therapy(s) that the targetpopulation would receive currently (status quo – including best supportive care; dose, frequency, treatment duration/conditions for treatment cessation). **O**utcomes: Details the key therapeutic outcome(s), including therapeutic intent, outcome definitions, timeframes to achieve outcome(s), and source of outcome data.	

9. Risdiplam (Evrysdi) for the treatment of pre-symptomatic spinal muscular atrophy (SMA)

Application

9.1. The Advisory Committees reviewed the application for risdiplam (Evrysdi) for the treatment of pre-symptomatic spinal muscular atrophy (SMA).

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

Recommendation

9.3. The Advisory Committees **recommended** that risdiplam for the pre-symptomatic treatment of SMA be listed with a **high priority** within the context of treatments for rare disorders, subject to the following Special Authority criteria (changes to current proposed criteria marked in bold):

Initial application – (spinal muscular atrophy (SMA)) from any relevant practitioner. Approvals valid for 12 months for applications meeting the following criteria:

All of the following:

1. Patient has genetic documentation of homozygous SMN1 gene deletion, homozygous SMN1 point mutation, or compound heterozygous mutation; and
2. Patient is 18 years of age or under; and
3. **Either:**
   - 3.1. Patient has experienced the defined signs and symptoms of SMA type I, II or IIIa prior to three years of age; or
   - 3.2. **Both:**
     - **3.2.1. Patient is pre-symptomatic; and**
     - **3.2.2. Patient has three or less copies of SMN2**

Renewal – (spinal muscular atrophy (SMA) from any relevant practitioner. Approvals valid for 12 months for applications meeting the following criteria:

Both of the following**:**

1. There has been demonstrated maintenance of motor milestone function since treatment initiation; and
2. Patient does not require invasive permanent ventilation (≧at least 16 hours per day) in the absence of a potentially reversible cause while being treated with risdiplam

3. Risdiplam not to be administered in combination other SMA disease modifying treatments or gene therapy

9.4. In making this recommendation the Committees considered:

- That individuals with pre-symptomatic SMA had the greatest potential to benefit from treatment with risdiplam;
- That it is currently considered that both risdiplam and nusinersen have similar clinical effects on SMA;
- That there are individuals diagnosed with pre-symptomatic SMA for whom treatment with nusinersen is unsuitable. This may include those who live in rural areas where access to institutional treatment with nusinersen may be a barrier to treatment access;
- That risdiplam has suitability advantages over nusinersen as it is an oral, at home treatment rather than an intrathecal treatment.

Discussion

Māori impact

9.5. The Committees discussed the impact of funding risdiplam for the treatment of pre-symptomatic SMA on Māori health areas of focus and Māori health outcomes. The Committees noted the lower reported prevalence and incidence of SMA in Māori, and considered the presence of a mutation in the *SMN1* gene does not appear to be associated with or influenced by ethnicity. However, the Committee considered that there is inequitable access to obstetric and early postnatal care, as well as a lack of health literacy and support from culturally appropriate health care workers that could impact on Māori access to newborn screening, resulting in lower access to screening, and consequently lower access to more efficacious pre-symptomatic treatment. The Committees noted that SMA is not included as a Māori health area of focus in Te Whaioranga, Pharmac's Māori responsiveness strategy.

Background

9.6. The Committees noted that in September 2019, the Rare Disorders Subcommittee (now Specialist Advisory Committee) recommended nusinersen be funded with a high priority for the treatment of pre-symptomatic SMA in individuals with two or three SMN2 copies, subject to special authority criteria. The Committees noted that 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 individuals with pre-symptomatic SMA had the greatest potential to benefit from treatment.

9.7. The Committees noted that from 1 January 2023, nusinersen has been funded for pre-symptomatic SMA (as well as SMA types I, II, or IIIa).

9.8. The Committees noted that in March 2021, the Rare Disorders and Neurological Subcommittees recommended that risdiplam for the treatment of type I SMA be listed with a high priority and deferred a recommendation for the funding of risdiplam for types II and III. The Committees noted that in August 2021 PTAC recommended that risdiplam for the treatment of type I spinal muscular atrophy be listed with a high priority and recommended that risdiplam for the treatment of types II and IIIa spinal muscular atrophy (aged 18 years and under) be listed with a medium priority. In July 2021 the Rare Disorders and Neurological Subcommittees recommended that risdiplam for the treatment of types II and III SMA (in individuals aged under 25 years) with a high priority, following the review of further evidence.

9.9. The Committees noted that at the time of the meeting, Pharmac was reviewing consultation feedback on a proposal to fund risdiplam from 1 May 2023 for the

treatment of SMA types I, II, and IIIa for people who start treatment when they're 18 years old and younger.

Health need

9.10. The Committees noted that the health need of people with pre-symptomatic SMA has been considered in previous clinical advice meetings. The Committees re-iterated that pre-symptomatic individuals are likely to gain the greatest benefits from SMA treatment, due to minimising the number of motor neurones lost and associated level of lost physical functionality

9.11. The Committees noted that individuals who are pre-symptomatic are unable to be classified as type I, II, III or IV, which are defined based on time of symptom onset; and so are classified by the number of SMN2 copies, due to current evidence indicating that number of SMN2 copies correlating inversely with disease severity.

9.12. The Committees considered that approximately 90% of SMA cases are able to be diagnosed by local testing of exon 7 deletion of chromosome 5q, and that this estimation as calculated is in line with MSAC calculations in Australia. The Committees noted that in cases with negative test results but high clinical suspicion, the more accurate *SMN1* gene sequencing test can be requested from the Victorian Clinical Genetic Service in Australia. The Committees noted the specificity of local genetic testing (near 100%) and high sensitivity (90% x 85% = 76.5%).

9.13. The Committees noted that approximately 85% of people with SMA types I, II or III had less than or equal to 3 *SMN2* copies, in a study of 272 patients (Calucho et al. Neuromuscular Disorders. 2018;28(3):208-15), meaning that approximately four people per year would be expected to be diagnosed pre-symptomatically with a threshold of three SMN2 copies. The Committees noted the distribution of *SMN2* copy numbers according to SMA type in Calucho et al. – of 625 participants with SMA, 8.15% of participants with SMA Type III had four copies of *SMN2*. All other participants with Type 3 SMA, as well as all participants with Types 1 and 2 SMA, had 3 or less copies of *SMN2*.

9.14. The Committees considered that if the proposed funding criteria for risdiplam limits the number of *SMN2* copies to 3 as per the current nusinersen funding criteria, then some individuals with Type 3 SMA may be missed at the time of screening. Members considered that the proposed funding criteria increased the limit number of *SMN2* copies to 4, then some individuals would be treated pre-symptomatically – who otherwise would manifest SMA type IIIb or IV (who would not otherwise be eligible for treatment), or may never become symptomatic.

9.15. The Committees noted that based on previous consideration by PTAC and the Rare Disorders and Neurological Subcommittees, a large proportion of people with SMA would be assumed to have an SMA type IV phenotype if treated in the pre-symptomatic setting. The Committees considered it important that the morbidity associated with an SMA type IV phenotype be reflected in economic modelling in the decades after symptom onset with this phenotype, given the recommended assumption of lifelong benefit.

9.16. The Committees discussed the impact of funding risdiplam for the treatment of pre-symptomatic SMA on Māori health areas of focus and Māori health outcomes. The Committees noted the lower reported prevalence and incidence of SMA in Māori, and considered the presence of a mutation in the *SMN1* gene does not appear to be associated with or influenced by ethnicity. The Committees noted that SMA is not included as a Māori health area of focus in Te Whaioranga, Pharmac Māori responsiveness strategy.

9.17. The Committees noted that routine screen of all newborns for SMA is not currently routinely available in New Zealand; however, that following the funding of nusinersen, this may be developed. The Committees noted that access to and utilisation of screening would not be changed with the addition of risdiplam as a treatment option in the pre-symptomatic setting.

Health Benefit

9.18. The Committees noted that Medsafe has approved the use of risdiplam in people aged two months and over and that further assessment is currently underway to extend the indication to remove the age restriction. The Committees noted that all infants included in the RAINBOWFISH study were under two months old, and that the youngest started treatment at 28.5 days old.

9.19. The Committees noted the 12-month interim results of the RAINBOWFISH trial, an open label study of infants with genetically diagnosed and pre-symptomatic SMA (Finkel et al. Cure SMA 2022 presentation on behalf of the RAINBOWFISH study group, sponsored by Roche. Anaheim, USA; 2022 June 16).

9.19.1. The Committees noted that at the cut-off for interim data, seven infants had been treated with risdiplam for 12 months or more. Four infants had two *SMN2* copies, and three had >2 *SMN2* copies (number of copies not further defined). The Committees noted the mean HINE-2 score change from baseline was 18.75. All infants were sitting without support, six patients achieved the highest levels of rolling (supine to prone), and five infants were walking independently. All included infants maintained the ability to swallow and were able to feed exclusively by mouth.

9.19.2. The Committees noted the investigator's report concluded that adverse events (AEs) were more reflective of the age of the infants rather than the underlying SMA, or treatment with risdiplam. The Committees noted that at 12 months no deaths, no serious AEs, or AEs that led to treatment withdrawal or discontinuation were reported. Members noted that unlike nusinersen, which is administered as an intrathecal injection, risdiplam does not carry the risks associated with intrathecal injection and sedation.

9.20. The Committees noted that there are currently no direct head-to-head trials of nusinersen and risdiplam in the pre-symptomatic setting. The Committees considered that while patient numbers in trials for each medicine are relatively small, which makes them difficult to compare, it is currently considered that both risdiplam and nusinersen have similar clinical effects on SMA. Members considered, that based on the similar mechanisms of action, this was biologically plausible.

9.21. The Committees considered that once new-born screening for SMA was in place, most individuals would be diagnosed and begin treatment pre-symptomatically. Members considered that this would provide additional treatment benefit in comparison to treatment initiation after the onset of symptoms.

Suitability

9.22. The Committees noted that risdiplam is a once daily oral medication, presented as a powder for reconstitution with purified or sterile water which is to be reconstituted by a healthcare professional. The Committees noted that risdiplam can also be given via nasogastric tube, or gastrostomy.

9.23. The Committees considered that not being required to travel to hospital for intrathecal treatment (as with nusinersen) was a clear suitability benefit for risdiplam, particularly for individuals who live in rural areas and may find accessing clinical centres for nusinersen treatment difficult.

Cost and savings

9.24. The Committees considered that eventually 90% of those with pre-symptomatic SMA would initiate treatment with risdiplam preferentially to treatment with nusinersen, due to the suitability of oral treatment compared with repeated intrathecal injections. The Committees noted that this was supported by a recent discrete choice experiment conducted with patients and caregivers of patients with SMA (Monnette et al. Orphanet J Rare Dis. 2021;16:36).

9.25. The Committees considered that there would be a cost associated with implementing a national screening service for SMA, but that this cost would be incurred regardless of the funding of risdiplam, as nusinersen has been funded for this indication already.

9.26. The Committees considered that, compared with nusinersen intrathecal injection treatment for SMA, oral risdiplam has the potential to reduce health system costs to a greater extent, with the same or similar efficacy likely to be achieved.

Summary for assessment

9.27. The Advisory Committees considered that the below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for risdiplam if it were to be funded in New Zealand for pre-symptomatic treatment of SMA. This PICO captures key clinical aspects of the proposal and may be used to frame any future economic assessment by Pharmac staff. This PICO is based on the Advisory Committees' assessment at this time and may differ from that requested by the applicant. The PICO may change based on new information, additional clinical advice, or further analysis by Pharmac staff.

9.28. The Committees noted that the PICO table below was relevant for all individuals with SMA not just those who will be diagnosed pre-symptomatically. The Committees also noted that the intervention would commence when individuals were less than 2 months old.

<table>
<tr><td>Population</td><td colspan="2">As defined in the special authority criteria above, people with ≤ 3 SMN2 gene copies, who are ≤ 18 years of age, and have genetic documentation of: homozygous SMN1 gene deletion, homozygous SMN1 point mutation, or compound heterozygous mutation.</td></tr>
<tr><td rowspan="4">Intervention</td><td colspan="2">Risdiplam once daily oral dose as determined by age and body weight</td></tr>
<tr><td>Age and body weight</td><td>Recommended daily dose</td></tr>
<tr><td>2 months to < 2 years of age</td><td>0.20 mg/kg</td></tr>
<tr><td>≥ 2 years of age (< 20 kg)</td><td>0.25 mg/kg</td></tr>
<tr><td>Comparator(s) (NZ context)</td><td colspan="2">• 56% nusinersen in the first year of funding (increasing over time) – one vial per treatment
• 44% best supportive care in the first year (reducing over time)</td></tr>
</table>

Outcome(s)	• Motor function (including, where applicable, age-appropriate motor milestones such as sitting, standing and walking) • Bulbar function (including, for example, swallowing and ability to communicate) • Frequency and duration of hospitalisation • Respiratory function • Complications of spinal muscular atrophy (including, for example, scoliosis and muscle contractures) • Need for non-invasive or invasive ventilation • Stamina and fatigue • Mortality • Adverse effects of treatment • Health-related quality of life

Table definitions:

Population: The target population for the pharmaceutical, including any population defining characteristics (eg line of therapy, disease subgroup)

Intervention: Details of the intervention pharmaceutical (dose, frequency, treatment duration/conditions for treatment cessation).

Comparator: Details the therapy(s) that the patient population would receive currently (status quo – including best supportive care; dose, frequency, treatment duration/conditions for treatment cessation).

Outcomes: Details the key therapeutic outcome(s), including therapeutic intent, outcome definitions, timeframes to achieve outcome(s), and source of outcome data.

10. Onasemnogene abeparvovec in the treatment of pre-symptomatic or type 1 spinal muscular atrophy (SMA)

Application

10.1. The Advisory Committees reviewed the application for onasemnogene abeparvovec in the treatment of pre-symptomatic or type 1 spinal muscular atrophy (SMA).

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

Recommendation

10.3. The Advisory Committees **recommended** that onasemnogene abeparvovec be **deferred** for the treatment of pre-symptomatic or type 1 SMA within the context of treatments for rare disorders and for neurological disorders, until further evidence regarding longevity of the therapeutic benefit and safety becomes available.

10.4. Advisory Committees noted in making this recommendation that additional long-term real-world data, as well as Phase 3 trial cohort follow ups would provide greater confidence on the expected duration of the health benefits and risks associated with individuals being treated with onasemnogene abeparvovec.

Discussion

Māori impact

10.5. The Committees discussed the impact of funding onasemnogene abeparvovec for the treatment of SMA on Māori health areas of focus and Māori health outcomes. The Committees noted that those who are diagnosed prior to symptoms (presymptomatic) often have the best clinical outcomes. At present there is inequitable access to obstetric and early postnatal care, as well as a lack of health literacy and support from culturally appropriate health care workers that could impact on Māori access to

newborn screening, risking lower access to screening, and consequently lower access to more efficacious pre-symptomatic treatment.

10.6. The Committees noted people of Māori and Pacific ethnicity are overrepresented amongst individuals with SMA who remain living and resident in New Zealand.

10.7. The Committees considered unpublished 2023 reporting by Richard Roxburgh and colleagues that Māori had a lower prevalence of SMA than the general New Zealand population (0.34 vs. 1.78 per 100,000 live births).

Background

10.8. The Committees noted that this is a new application for onasemnogene abeparvovec, a gene therapy for the treatment of presymptomatic or symptomatic type 1 SMA.

10.9. The Committees noted that this is the first gene therapy considered for this indication.

10.10. The Committees noted that other therapies including nusinersen and risdiplam have been considered for SMA previously.

Health need

10.11. The Committees noted that SMA is a rare autosomal recessive neuromuscular condition, that can be classified into subtypes by disease severity:

- Type 0: prenatal onset
- Type 1: infantile onset (<6 months)
- Type 2: 6-18 months age of onset
- Type 3: subdivided by age of onset (3a <3 years; 3b 3-12 years; 3c 12-18 years)
- Type 4: adult onset

10.12. The Committees noted that the less severe forms of disease (types 3 and 4) are more prevalent than the more severe forms of disease (types 0,1 and 2). Whilst all types of SMA have similar incidence, those with less severe forms have a greater life expectancy and therefore there is a higher prevalence.

10.13. The Committees noted that in those with SMA type 1, those affected are unable to sit or roll, with muscle weakness worsening with age, and eventually affecting swallowing and breathing. The life expectancy of those affected is less than 2 years. In addition, the Committees noted that there is a high need for hospitalisation during the treatment of those affected by type 1 SMA, including feeding and respiratory support, as well as palliative care.

10.14. The Committees noted that supportive care includes non-pharmaceutical interventions such as physiotherapy and nutritional support.

10.15. The Committees noted that at least one of the parents of an individual with type 1 SMA is likely to be a full-time carer for the child and can be at risk of a possible injury due to the physical requirements of the care. The Committees noted an Australian study of SMA caregivers, where 78% reported problems with their own physical health, and 84% reported problems with their own mental health, regardless of the SMA type of the person they cared for (Chambers et al. Neurology. 2020;95(1):e1-e7).The Committees noted the psychological impact on the whānau, as well as potential implications on family planning.

10.16. The Committee noted that from 1 January 2023, nusinersen has been funded for people (aged 18 years and under at time of treatment initiation) with pre-symptomatic SMA and types 1-3a. The Committees noted that the renewal criteria for nusinersen

include a requirement for treatment to not be administered in combination with other SMA disease modifying treatments or gene therapy.

10.17. The Committees noted that the mutation in the *SMN1* gene does not appear to be affected by ethnicity, however, the number of families of Māori and Pacific ethnicity are now overrepresented amongst those caring for individuals with SMA who remain living and resident in New Zealand. The Committees noted unpublished 2023 reporting by Richard Roxburgh and colleagues that Māori had a lower prevalence of SMA than the general New Zealand population (0.34 vs. 1.78 per 100,000 live births).

10.18. The Committees noted Māori generally have poorer access to healthcare, and while access to healthcare is unlikely to have influenced the rates of early onset, severe disease, it may influence diagnosis rates at the milder end of the spectrum. In addition, access to healthcare may also affect length of survival in the more severe types of SMA.

Health benefit

10.19. The Committees noted the mechanism of action of onasemnogene abeparvovec, with an adeno-associated virus (AAV) based delivery system that is targeted to motor neuron cells, providing a copy of the *SMN* gene to the cell nucleus that can form a circular episome, that persists in the nucleus of cells, and can provide a continuous expression of the *SMN* gene. The Committees noted that an episome is formed and therefore there is minimal evidence of integration into the human genome. In addition, the Committees noted that *SMN* expression is in the motor neurones and peripheral tissues, with onasemnogene abeparvovec able to cross the blood brain barrier.

10.20. The Committees noted that onasemnogene abeparvovec is currently undergoing initial evaluation by Medsafe for regulatory approval.

10.21. The Committees considered the Mendell J.R. et al, N Engl J Med. 2017 2;377:1713-22 study that reported the findings from the START trial, a phase 1, open-label, dose-escalation study. The study enrolled individuals who had SMA type 1 with 2 copies of SMN2 gene. A total of 15 were treated, with 12 administered the therapeutic dose and 3 the subtherapeutic dose. The primary objective was safety, and 56 serious adverse events were reported in 13 people. There were 2 treatment related grade 4 events, and 4 individuals had an increase in aspartate transaminase and alanine aminotransferase which were successfully treated with prednisolone. Secondary objectives were time to death or permanent ventilation, with no individual requiring permanent ventilatory assistance, 1 in the subtherapeutic dose required permanent ventilation due to hypersalivation. Non-invasive ventilation was reduced by 25% to 15 hours per day after salivary-gland ligation. In the subtherapeutic dose group there was a mean increase of 7.7 points from a baseline of 16.3 in The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) score, whilst in the high dose group there was a 24.6-point mean increase from baseline of 28.2. In the therapeutic dose cohort 11/12 could sit unassisted ≥5 seconds, n=10 for ≥10 seconds, and n=9 for ≥30 seconds. A total of 11 individuals achieved head control, 9 could roll over, and 2 could crawl, pull to stand, stand independently, and walk independently. In the study, 11 attained the ability to speak, whilst 7/12 were independent of ventilatory assistance at the last follow-up visit compared to 10/12 at baseline. A total of 11/12 achieved or retained the ability to swallow independently, and 4 were able to feed orally. The Committees considered the Al-Zaidy S et al, Pediatr Pulmonol. 2019;54:179-85 and Mendell et al, JAMA Neurol. 2021;78:834-41 studies that provided 2 and 5 year follow up data respectively. All individuals who continued to 5 years (n=13) were alive without the need for permanent ventilation. All individuals (n=10) maintained previously acquired motor milestones, whilst 2 achieved new standing with assistance. Severe adverse events occurred in 8 individuals (62%), including acute respiratory failure (31%), pneumonia (31%),

dehydration (23%), respiratory distress (15%) and bronchiolitis (15%). At 5 years post dosing, 7/13 were receiving concomitant nusinersen, including 3 who received a subtherapeutic dose and 4 who received the therapeutic dose, to maximise benefit.

10.22. The Committees considered the Lowes et al, Pediatr Neurol. 2019;98:39-4 study, which provided further analysis from the START trial. Children were grouped by age at dosing as well as baseline CHOP-Intend scores. The study reported that those with lower CHOP-Intend scores, who were dosed earlier, had greater increases in mean points gained (35 points improvement from a mean baseline of 15.7). Those that had later dosing had a mean gain of 23.3 points (from a mean baseline of 26.5), whilst those who had higher CHOP-Intend scores but were dosed earlier quickly reached a mean score of 60.3 points, near the scale maximum (64), from a mean baseline of 44.0.

10.23. The Committees considered the STR1VE US (n=22, treated at aged less than 6 months) and EU (n=32 study aged less than 6 months) studies reported in Day et al, Lancet Neurol. 2021;20:284-293 and Mercuri et al, Lancet Neurol. 2021;20:832-41 respectively. The Committees noted that these were both phase 3, open label, single-arm studies in those with SMA type 1, with two copies of the *SMN2* gene. The Committees noted that there were subtle differences in the eligibility criteria, with the population enrolled on the EU trial more symptomatic, and therefore recording lower baseline CHOP-INTEND scores. The Committees noted that the 2 trials were therefore not directly comparable. The Committees noted that all people who were enrolled improved from their baseline scores, however the EU cohort showed a lower improvement which was hypothesised to be due to the EU individuals having a lower CHOP-INTEND scores at enrolment. In those in the US study 59% (13/22) could sit for greater than 30 seconds, whilst 91% survived free from permanent ventilation at 18 months and 14 months post dosing respectively. In the EU study 44% (14/32) could sit for greater than 10 seconds and 97% survived free from permanent ventilatory support at 18 and 14 months respectively. The study reported 3 serious adverse events that were related or possibly related to treatment in the US, whilst there were 6 in the EU cohort. The Committees noted that a sit test time of greater than 30 seconds is more clinically relevant than shorter timeframes.

10.24. The Committees considered the SPR1NT 1 study reported in Strauss et al, Nat Med, 2022 28, 1381-89 . A total of 14 individuals with pre symptomatic SMA with 2 *SMN2* gene copies were treated at less than 6 weeks old. At the end of the study (18 months), all could sit independently for at least 10 seconds at any study visit, as well as achieved the motor milestones as defined by both the Bayley-III Scales of Infant and Toddler Development (BSID) and the WHO Multicentre Growth Reference Study (WHO-MGRS). A total of 79% of children stood alone, whilst 50% stood within the normal developmental window of ≤514 days. All survived without permanent ventilation. A total of 13 (93%) treated maintained weight at or above the third percentile without non-oral/mechanical feeding support up to 18 months of age. Each child experienced at least 1 treatment emergent adverse event, and 5 (36%) had at least 11 treatment emergent adverse event deemed to be serious.

10.25. The Committees considered data from SPR1NT 3 study reported in Strauss et al Nat Med 2022;28,1390-97. The study was a phase 3, multicentre, single-arm trial in those with pre-symptomatic SMA with 3 copies of the *SMN2* gene (n=15). All those enrolled were alive and free from permanent ventilation. Similarly, all enrolled stood for ≥3 seconds at any visit up to 24 months of age and maintained the milestone until the 24-month visit. At the 24 months study visit, 14 (93%) walked independently for at least five steps. Each child had ≥ 1 treatment emergent adverse event, and 3 had a treatment emergent adverse event reported as serious.

10.26. The Committees considered a meta-analysis from Pascual-Morena et al, Hum Gene Ther. 2022 that analysed data to estimate the effect of onasemnogene abeparvovec on motor function in participants with type 1 SMA. A total of 11 studies were included in the systematic review, and 4 in the meta-analyses. The analysis found that onasemnogene abeparvovec improved CHOP-INTEND scores by 11.06 (9.47, 12.65) and 14.14 (12.42, 15.86) points at 3- and 6-months post-infusion, respectively. A total of 87%, 51%, and 12% achieved CHOP-INTEND scores of >40, >50, and >58/60 points, respectively. However, this proportion increased to 100% in pre-symptomatic participants with greater baseline CHOP-INTEND. Motor milestones were also improved, especially in pre-symptomatic participants.

10.27. The Committees noted that the pivotal trials include well-chosen endpoints, however noted that the risk and benefits in long term data remain unclear due to the low number enrolled in the trials, as well as short durations of follow up.

10.28. The Committees also considered evidence from:

- Deepa et al, Pediatric Neuro, 132, 2022, 27-32
- Weiß et al, The Lancet Child Adolesc Health, 2022, 6, 17-27
- Bischof et al, Curr Med Res Opin. 2021; 37:1719-1730
- Chand et al, J Hepatol. 2021; 74:560-566
- D'Silva et al, Ann Clin Transl Neurol. 2022;9:339-350
- Bitetti et al, Gene Ther. 2022
- Lee et al, Brain Dev. 2022;44:287-293
- Friese et al, J Neuromuscul Dis. 2021;8:209-216
- Tosi et al, Acta Myol. 2022;41:117-120

10.29. The Committees noted that there may be a future loss in skills acquired through treatment, as a person grows, due to the one-time nature of the treatment. The Committees noted that this would be identified through long term follow up. The Committees also noted that several studies reported individuals accessing a second therapeutic agent alongside onasemnogene abeparvovec.

10.30. Some Committee members noted that gene therapies are a relatively new technology with many awaiting long-term safety outcome data. Risks associated with them include allergic reactions, damage to organs or tissues or developing cancers. The Committee noted that individuals/caregivers/guardians need satisfactory disclosure around the uncertainty with these risks and their consequences.

Suitability

10.31. The Committees noted that onasemnogene abeparvovec was a one-time treatment requiring intravenous infusion, that required short term pre and post dose treatment with prednisolone. The Committees noted that this was less intensive on the individual in comparison to nusinersen, which required regular intrathecal administration for life, or risdiplam which required oral medication daily for life. The Committees also noted that nusinersen may require sedation or anaesthesia to administer and may be impossible to administer to those with scoliosis.

10.32. The Committee noted that an extended hospital stay for monitoring may be necessary and would represent an additional stressor to individuals and their families.

Cost and saving

10.33. The Committees noted that there may be a cost to establish specialised preparation rooms within infusion centres that can administer gene therapies.

10.34. The Committees noted that there are additional costs to the family of a child that has SMA (beyond SMA treatments' costs), including lost income through restricted work hours, as well as the psychological impact. The Committees considered the study by Dangouloff et al. Dev Med Child Neurol. 2023;65:67-77 which reviewed the financial and quality of life impact of SMA on parents.

10.35. The Committees considered the evidence of the benefit of onasemnogene abeparvovec to be promising in the short term, especially with pre-symptomatic treatment. However, the evidence of long-term efficacy was considered too uncertain to support modelling of a treatment effect lasting a full lifetime. Given the duration of available evidence, and use of other disease modifying treatments after onasemnogene abeparvovec in some studies in relevant groups, the Committees considered the comparability of treatment effect with nusinersen or risdiplam uncertain.

10.36. The Committees noted that the cost effectiveness of onasemnogene abeparvovec was limited in the absence of evidence supporting a lifetime treatment effect or superiority to the currently funded treatment, nusinersen, in terms of health-related quality of life gains or survival. Given the deferral recommendation, the Committees noted that treatment benefit assumptions would be revisited once Special Authority criteria had been agreed to define the group of individuals eligible for onasemnogene abeparvovec.

10.37. The Committees noted that there may be increased ongoing costs to the healthcare system supporting people to live longer lives, though that the intensity of costs may be lower as people remained healthier for longer. The Committees noted that in the cost utility analysis, these would be considered alongside the benefit for individuals receiving treatment.

10.38. The Committees considered that 90% uptake would be reasonable, however also noted that this was highly uncertain given ambiguity around patient attitudes towards novel treatments, and that funding onasemnogene abeparvovec may require additional health education for individuals or their carers to make informed decisions about treatment.

10.39. The Committees noted that other countries limited gene therapy usage to specific centres, which have specialised facilities to prepare the infusion, which may need to be established in New Zealand for onasemnogene abeparvovec to be administered.

Funding criteria

10.40. The Committees noted that other countries have restricted the use of onasemnogene abeparvovec to those under the age of 6 months. In addition, the Committees noted the lack of safety and health benefit evidence for those over 13.5kg in weight.

Summary for assessment

10.41. The Advisory Committees considered that the below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for onasemnogene abeparvovec if it were to be funded in New Zealand for presymptomatic and type 1 SMA. This PICO captures key clinical aspects of the proposal and may be used to frame any future economic assessment by Pharmac staff. This PICO is based on the Advisory Committees' assessment at this time and may differ from that requested by the applicant. The PICO may change based on new information, additional clinical advice, or further analysis by Pharmac staff.

Population	• People with SMA type I who have been diagnosed symptomatically. • People with pre-symptomatically diagnosed SMA who have ≤3 *SMN2* gene copies.
Intervention	Onasemnogene abeparvovec, at the recommended dose of Zolgensma is 1.1 × 10E14 vector genomes (vg)/kg as a one-time (or 'one off') treatment. The Zolgensma kit consists of 2 vial sizes (either 5.5 mL or 8.3 mL). All vials have a nominal concentration of 2.0 × 10E13 vg/mL. The appropriate Zolgensma dose and kit is determined by an individual's body weight.
Comparator(s) (NZ context) [funded SMA treatments at the time of the meeting]	Nusinersen – four doses in the first year of treatment, three doses in subsequent years of treatment. Each dose is one single-use vial of 12 mg nusinersen equivalent, administered via intra-thecal injection.
Outcome(s)	• Motor function (including, where applicable, age-appropriate motor milestones such as sitting, standing and walking) • Bulbar function (including, for example, swallowing and ability to communicate) • Frequency and duration of hospitalisation • Respiratory function • Complications of spinal muscular atrophy (including, for example, scoliosis and muscle contractures) • Need for non-invasive or invasive ventilation • Stamina and fatigue • Premature mortality • Adverse effects of treatment • Health-related quality of life

Table definitions:

Population: The target population for the pharmaceutical, including any population defining characteristics (eg line of therapy, disease subgroup)

Intervention: Details of the intervention pharmaceutical (dose, frequency, treatment duration/conditions for treatment cessation).

Comparator: Details the therapy(s) that the target population would receive currently (status quo – including best supportive care; dose, frequency, treatment duration/conditions for treatment cessation).

Outcomes: Details the key therapeutic outcome(s), including therapeutic intent, outcome definitions, timeframes to achieve outcome(s), and source of outcome data.