Record of the Rare Disorders Subcommittee meeting held at PHARMAC on 5 and 6 November 2018 (minutes for web publishing)

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

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

The Rare Disorders Subcommittee may:

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

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

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

These Subcommittee minutes will be reviewed by PTAC at its February 2019 meeting.

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4. Carglumic Acid for the treatment of hyperammonaemia due to urea cycle disorders and organic acidaemias

Applications

4.1. The Subcommittee reviewed three applications for the funding of carglumic acid for the treatment of hyperammonaemia:

4.1.1. A clinician application for carglumic acid for the treatment of hyperammonaemia due to urea cycle disorders and organic acidaemias.

4.1.2. An application from Max Health Ltd for carglumic acid (Ucedane) for the treatment of hyperammonaemia due to N-acetylglutamate synthase deficiency and organic acidaemias.

4.1.3. An application from TeArai BioFarma for carglumic acid (Carglumic Acid Dipharma) for the treatment of organic hyperammonaemias.

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

Recommendations

4.3. The Subcommittee **recommended** that carglumic acid be funded with a **high** priority for the treatment of hyperammonaemia due to carbamoyl phosphate synthetase 1 (CPS1) or N-acetylglutamate synthase (NAGS) deficiency based on high health need, a lack of treatment options, and moderate evidence of benefit, subject to the following Special Authority criteria:

Initial application – (carbamoyl phosphate synthetase 1 deficiency or N-acetylglutamate synthase deficiency) only from a metabolic physician. Approvals valid for 12 months for applications meeting the following criteria.
All of the following:
1. Either:
    1.1. Patient has hyperammonaemia due to N-acetylglutamate synthase deficiency; or
    1.2. Patients has hyperammonaemia due to carbamoyl phosphate synthetase 1 deficiency; and
2. Carglumic acid dose to be no greater than 250 mg/kg titrated to target ammonia levels.

Renewal (carbamoyl phosphate synthetase 1 deficiency or N-acetylglutamate synthase deficiency) only from a metabolic physician or any relevant practitioner on the recommendation of a metabolic physician. Approvals valid for 12 months where the treatment remains appropriate and the patient is benefitting from treatment.

4.4. The Subcommittee **recommended** that carglumic acid be funded with a **medium** priority for the short-term treatment of hyperammonaemia during an acute decompensation episode due to organic acidaemias, based on high health need and moderate evidence of benefit, subject to the following Special Authority criteria:

Initial application – (organic acidaemias) only from a metabolic physician. Approvals valid for 12 months for applications meeting the following criteria.

All of the following:

1. Patient has hyperammonaemia due to isovaleric acidaemia, methymalonic acidaemia, or propionic acidaemia; and
2. Carglumic acid to be used for acute management of hyperammonaemia related to acute metabolic decompensation; and
3. Carglumic acid dose to be no greater than 250mg/kg/day, titrated to target ammonia levels for a maximum of 15 days at a time; and
4. Treatment with ammonia scavenging medications is inadequate.

Renewal (organic acidaemias) only from a metabolic physician or any relevant practitioner on the recommendation of a metabolic physician. Approvals valid for 12 months for applications meeting the following criteria.

All of the following:

1. Patient has required no more the 12 short intermittent courses of carglumic acid to manage acute metabolic decompensation within the last 12 months; and
2. Treatment remains appropriate and the patient is benefitting from treatment.

Discussion

4.5. The Subcommittee noted that hyperammonaemia occurs when the body is unable to effectively transform ammonia into urea via the urea cycle. The Subcommittee noted that the applications for carglumic acid considered hyperammonaemia resulting from two different underlying conditions: urea cycle disorders (specifically N-acetylglutamate synthase [NAGS] deficiency and carbamoyl phosphate synthetase 1 [CPS] deficiency), and the classical organic acidaemias.

4.6. The Subcommittee noted that NAGS deficiency and CPS1 deficiency are inherited urea cycle disorders which result in a reduced ability to convert ammonia to carbamoyl phosphate, resulting in hyperammonaemia.

4.7. The Subcommittee noted that there are three classical organic acidaemias: isovaleric acidaemia (IVA), methymalonic acidaemia (MMA), and propionic acidaemia (PA). The Subcommittee noted that in these conditions, propionyl CoA, methylmalonyl CoA, or isovaleryl CoA accumulate over time to inhibit NAGS, resulting in episodes of acute metabolic decompensation which can lead to hyperammonaemia.

4.8. The Subcommittee noted that the age of onset and severity of symptoms of urea cycle disorders and organic acidaemias varies depending on the specific enzyme affected and the degree of dysfunction of the enzyme. The Subcommittee noted that some patients may have no residual enzyme activity.

4.9. The Subcommittee noted that individuals with severe cases of hyperammonaemia due to NAGS deficiency, CPS1 deficiency, or organic acidaemias present in early childhood with symptoms including vomiting, poor appetite, food refusal, and protein aversion; and that long-term effects can include failure to thrive, learning disabilities, neurodevelopmental delay, hepatomegaly, psychiatric symptoms, and death.

4.10. The Subcommittee noted that the health need for patients with NAGS deficiency, CPS1 deficiency, and classical organic acidaemias is high; patients are at lifelong risk of metabolic decompensation and intercurrent hyperammonaemia.

4.11. The Subcommittee noted a longitudinal study of 614 patients with urea cycle disorders which reported a neonatal mortality rate of 24% and a mortality rate for late-onset cases of 11% (Batshaw et al. Mol Genet Metab. 2014;113:127-30).

4.12. The Subcommittee noted that PHARMAC staff are aware of one patient in New Zealand who has been diagnosed with CPS1 deficiency and no patients with NAGS deficiency. The Subcommittee noted that data from the New Zealand newborn screening programme indicates that there are at least 10 individuals in New Zealand with the classical organic acidaemias (IVA, n = 5; MMA, n = 3; PA, n = 2) (Wilson et al. JIMD Rep. 2017;35:53-58). The Subcommittee considered that these data indicate that the prevalence of hyperammonaemia due to NAGS or CPS1 deficiencies or organic acidaemias is cumulatively less than 1:50,000.

4.13. The Subcommittee noted that carglumic acid is not currently approved by Medsafe, but that carglumic acid (Carbaglu) has received regulatory approval in the EU and Australia for hyperammonaemia due to NAGS deficiency and organic acidaemias, and in the US and Canada for hyperammonaemia due to NAGS deficiency. The Subcommittee noted that Ucedane has gained regulatory approval in the EU, that Carglumic Acid Dipharma has not gained regulatory approval in any country to date, and that neither product has been submitted for regulatory approval in New Zealand. The Subcommittee noted that carglumic acid is not registered for any indication other than hyperammonaemia.

4.14. The Subcommittee considered that the funding application for carglumic acid met PHARMAC's principles for rare disorders (PHARMAC applied definition of a rare disorder).

4.15. The Subcommittee noted that current treatment options for hyperammonaemia due to NAGS or CPS1 deficiencies or organic acidaemias include a low protein diet, intravenous fluids (with or without lipids), intravenous glucose, ammonia scavenging medications (e.g. sodium benzoate, sodium phenylbutyrate), intravenous L-arginine and L-citrulline (depending on underlying diagnosis), and haemofiltration when treatment fails to sufficiently address hyperammonaemia. The Subcommittee considered that these treatments are likely to be insufficient for patients with severe urea cycle disorders or organic acidaemias; and that liver transplantation is the only curative option for these patients.

4.16. The Subcommittee noted that carglumic acid is a synthetic structural analogue of N-acetylglutamate (NAG), the naturally occurring activator of CPS1 which is the first enzyme in the urea cycle. The Subcommittee noted that carglumic acid acts as a replacement for NAG by activating CPS1.

4.17. The Subcommittee noted that carglumic acid is supplied as 200 mg dispersible tablets for administration either orally or via nasogastric tube. The Subcommittee noted that the initial recommended dose of carglumic acid is 100 mg/kg/day, or up to 250 mg/kg/day as needed in two to four divided doses; and that the recommended maintenance dosing is between 10 mg/kg/day and 100 mg/kg/day. The Subcommittee noted that carglumic acid has a bitter taste, which may be unpalatable when administered orally.

4.18. The Subcommittee noted that the evidence for the use of carglumic acid for the treatment of hyperammonaemia due to urea cycle disorders or organic acidaemias is of low quality and limited to small clinical trials, case studies, retrospective observational studies, and reviews. The Subcommittee noted that there are no randomised controlled trials that have

prospectively investigated the efficacy and safety of carglumic acid, and that it is unlikely that such trials will be conducted in the future.

4.19. The Subcommittee considered that the primary evidence for the use of carglumic acid for the treatment of hyperammonaemia due to NAGS deficiency is provided by a single review which included 25 articles: 1 controlled experimental study, 1 case series, 1 expert opinion, 3 animal studies, and 19 case reports (Häberle. Ther Clin Risk Manag. 2011;7:327-32). The Subcommittee noted that the included studies involved differing initiation, maintenance, and dosing protocols, and demonstrated variable morbidity and mortality depending on patient condition at initiation of treatment.

4.20. The Subcommittee noted that the review published by Häberle (2011) described long-term data available for 23 patients with NAGS deficiency who were treated with carglumic acid for between 7 and 249 months. The Subcommittee noted that, in these patients, plasma ammonia and glutamine normalised rapidly after the initiation of therapy and remained within normal limits during maintenance therapy, and that there was no deterioration in neurological or psychomotor outcome from baseline. The Subcommittee considered that carglumic acid was well tolerated by these patients, with only two treatment-related adverse events reported (bitter taste and hyperhidrosis).

4.21. The Subcommittee considered that the questions identified by Häberle (2011) regarding carglumic acid for the treatment of hyperammonaemia were relevant; namely, the concern regarding dosing regimen and whether adjunctive therapy or protein-restriction are required when treating with carglumic acid. The Subcommittee noted limitations of the study included the use of retrospective data and missing data.

4.22. The Subcommittee considered that the primary evidence for the use carglumic acid for the treatment of hyperammonaemia due to CPS1 deficiency is limited to a three-day trial of carglumic acid treatment in five patients with late-onset CPS1 deficiency (Ah Mew et al. J Pediatr. 2014;165:401-403). The Subcommittee noted that after three days of treatment, median plasma ammonia decreased from 115 to 82 µmol/L and four of five subjects demonstrated greater levels of ureagenesis. The Subcommittee noted that one patient who could not tolerate higher doses of sodium phenylbutyrate continued on longer-term carglumic acid treatment, resulting in clinical improvement due to improved urea cycle function.

4.23. The Subcommittee considered that the primary evidence for the use of carglumic acid for the treatment of hyperammonaemia due to organic acidaemias is provided by a retrospective, multicentre, open-label, uncontrolled, phase 3b observational study that was designed to evaluate the efficacy and safety of carglumic acid in patients with organic acidaemias with hyperammonaemia during metabolic decompensation episodes (Valayannopoulos et al. Orphanet J Rare Dis. 2016;11:32).

4.24. The Subcommittee noted that the study published by Valayannopoulos et al. (2016) included 41 patients (IA, n = 4; MMA, n = 21; PA, n = 16) with 48 decompensation episodes. The Subcommittee noted that the carglumic acid dosage was at the discretion of the physician, and that concomitant treatments were used during 44% of episodes.

4.25. The Subcommittee noted the study by Valayannopoulos et al. (2016) reported a mean (± standard deviation [SD]) baseline plasma ammonia concentration of 468.3 (±365.3) µmol/L in neonates and 171.3 (±75.7) µmol/L in non-neonates, and a mean (±SD) end-of-

treatment plasma ammonia concentration of 60.7 (±36.5) µmol/L (29 episodes) in neonates and 55.2 (±21.8) µmol/L (19 episodes) in non-neonates (normalisation defined as plasma ammonia concentration ≤60 µmol/L). The Subcommittee noted that the median time to ammonia normalisation was 38.4 hours in the neonate group and 28.3 hours in the non-neonate group, and that normalisation rates were similar between organic acidemia subgroups. The Subcommittee noted that the median time to ammonia normalisation was 1.5 days in patients receiving concomitant scavenger therapy and 1.6 days in patients who did not receive concomitant scavenger therapy.

4.26. The Subcommittee noted that in the study by Valayannopoulos et al. (2016), the clinical symptoms improved with carglumic acid therapy and there were no significant safety concerns. The Subcommittee noted that seven patients died due to serious adverse events that were considered to be related to the decompensation episode.

4.27. The Subcommittee considered that limitations of the study by Valayannopoulos et al. (2016) included a lack of control patients treated only with ammonia scavenging medications, patient data variability, the inability to adjust for cofounders, and the small number of patients in the subgroups analysed; however, the Subcommittee considered that despite these limitations, the study provided support for the use of carglumic acid for the treatment of hyperammonaemia during decompensation episodes for patients with classical organic acidaemias.

4.28. The Subcommittee considered a single-centre cohort study of 4 patients with PA and 4 patients with MMA is the only evidence for continuous use (for 7 to 16 months) of carglumic acid in organic acidaemias (Burlina et al. Mol Genet Metab Rep. 2016;8:34-40). Members considered the role of carglumic acid in the treatment of organic acidaemias is different to that of NAGs and CPS1 deficiencies and this impacts upon how it should be used. Members considered that for organic acidaemias, the limited evidence available indicates carglumic acid should be used to help manage hyperammonaemia during a decompensation episode in order to reduce the severity of acute decompensation rather than preventing decompensation episodes themselves, as there are other factors involved that contribute to decompensation in these patients.

4.29. The Subcommittee noted that applications for the funding of carglumic acid have been reviewed by several international health technology assessment agencies. The Subcommittee noted that Australia (PBAC) did not recommend funding carglumic acid for the treatment of hyperammonaemia, but that Scotland (SMC) has accepted carglumic acid for the treatment of hyperammonaemia due to NAGS deficiency and the classical organic acidaemias for use within NHS Scotland.

4.30. The Subcommittee noted that the applications from the suppliers were for generic versions of carglumic acid, and that only one of these suppliers had provided bioequivalence data. The Subcommittee considered that evidence of bioequivalence would be required to meet regulatory requirements; however, this would be considered by Medsafe. The Subcommittee noted the benefits of competition in the market given that generic versions of carglumic acid are available and considered that PHARMAC could consider the possibility of a competitive process if carglumic acid were to be funded.

4.31. The Subcommittee considered that if carglumic acid were to be funded, the cost per patient would vary significantly depending on dosage, duration of treatment, and whether carglumic acid would be used in conjunction or if it would replace alternative treatments

(e.g. ammonia scavenging agents). The Subcommittee also noted that the price proposed by the two suppliers for carglumic acid differed significantly.

4.32. The Subcommittee considered that there was potential for treatment with carglumic acid to reduce the number of hospitalisations caused by decompensated hyperammonaemia, prevent intensive care admissions, prevent liver transplants and haemodialysis, and reduce monitoring and specialist visit requirements.

4.33. The Subcommittee noted rapid cost-utility analysis conducted by PHARMAC for carglumic acid indicates the cost-effectiveness could vary widely depending on the indication, dose, and duration of treatment, in addition to cost. The Subcommittee considered that if treatment was limited to management of decompensation episodes or as a bridge therapy to liver transplant, then the cost effectiveness would likely improve significantly. Members noted that treatment with carglumic acid could stabilise patients with severe disease who would otherwise progress to liver transplant, and transplantation may no longer be required; however, life-long treatment with carglumic acid would then be necessary.

4.34. The Subcommittee considered that the evidence available to date indicates that patients with hyperammonaemia due to NAGS or CPS1 deficiencies have a high health need and may benefit from long-term treatment with carglumic acid. The Subcommittee also considered that patients with hyperammonaemia due to organic acidaemias have a high health need and may benefit from short-term treatment with carglumic acid during episodes of acute decompensation where ammonia scavenging medications have not been fully effective.

5. Elosulfase for the treatment of mucopolysaccharidosis type IVA (MPS IVA)

Application

5.1. The Subcommittee reviewed an application from BioMarin Pharmaceutical Australia Ltd for the funding of elosulfase alfa (Vimzim) for the treatment of mucopolysaccharidosis type IVA.

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

Recommendation

5.3. The Subcommittee **recommended** that the application for elosulfase alfa be **declined** based on uncertainty regarding the long-term benefit of treatment and the high proposed cost of the medicine.

Discussion

5.4. The Subcommittee noted that mucopolysaccharidosis type IVA (MPS IVA), also known as Morquio A syndrome, is an inherited disorder caused by a mutation in the gene that codes for N-acetylgalactosamine-6-sulfatase (GALNS), a lysosomal enzyme that degrades

glycosaminoglycans (GAGs) such as keratan sulphate and chondroitin-6-sulphate. The Subcommittee noted that a deficiency in GALNS results in the accumulation of GAGs within various body tissues, causing progressive organ dysfunction.

5.5. The Subcommittee noted that the characteristic features of MPS IVA include progressive skeletal dysplasia resulting in very short stature, musculoskeletal abnormalities, spinal cord compression, cardiorespiratory dysfunction, corneal clouding, hearing loss, dental abnormalities, and hepatomegaly. The Subcommittee noted that the severity of symptoms and rate of progression varies significantly between patients depending on the degree of dysfunction of GALNS.

5.6. The Subcommittee noted that MPS IVA is associated with significant morbidity, early mortality, and has a substantial impact on patient quality of life largely due to progressive loss of physical mobility and independence. The Subcommittee noted that patients may also experience both restrictive lung disease due to thoracic deformity and obstructive lung disease due to airway narrowing, as well as tracheal and bronchial abnormalities; these manifestations often result in dyspnoea and recurrent respiratory infections and can progress to respiratory failure.

5.7. The Subcommittee noted that in patients with severe phenotypes, linear growth is minimal after 6-7 years of age (generally, patients do not grow in height post the age of 2 years), and death usually occurs in the third or fourth decade of life due to cardiorespiratory failure. The Subcommittee noted that the average life expectancy of a patient with a severe MPS IVA phenotype is 25 years (±17 years). Members noted MPS IVA presents differently to other MPS syndromes with hypermobility and flexibility observed at the skeletal peripheries in patients with MPS IVA compared with the joint stiffness and contractures associated with other forms of MPS.

5.8. Members noted that individuals with MPS IVA have a severe health need which can result in a high emotional and psychological impact on families and puts a significant burden on caregivers.

5.9. The Subcommittee noted that there are currently only 5 individuals diagnosed with MPS IVA in New Zealand. The Subcommittee considered that the prevalence of MPS IVA is less than 1:50,000.

5.10. The Subcommittee noted that the current treatment paradigm for MPS IVA focuses on symptom management, which requires a multidisciplinary approach due to the broad spectrum of clinical manifestations. The Subcommittee noted that surgical interventions are often required to correct bone deformities, including spinal decompression/fusion surgery, corrective knee and hip surgery, and surgery to improve tracheal obstruction.

5.11. The Subcommittee noted that elosulfase alfa is a purified human enzyme produced using recombinant DNA technology that is intended to provide the exogenous enzyme GALNS to be taken up into the lysosomes in order to increase the catabolism of GAGs.

5.12. The Subcommittee noted that elosulfase alfa is approved by Medsafe for the treatment of MPS IVA in children and adults of all ages. The Subcommittee noted that elosulfase alfa is not indicated for the treatment of any other condition.

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

5.14. The Subcommittee noted that the recommended dosage of elosulfase alfa is 2 mg/kg of body weight administered via infusion once a week over a period of four hours.

5.15. The Subcommittee noted that applications for the funding of elosulfase alfa for the treatment of MPS IVA have been reviewed by several international health technology assessment agencies. The Subcommittee noted that Canada (CADTH) and Scotland (SMC) did not recommend the funding of elosulfase alfa, that Australia funds elosulfase alfa through the Life Saving Drugs Program, and that the UK (NICE) recommended to fund elosulfase alfa for the treatment of MPS IVA according to a managed access agreement.

5.16. The Subcommittee noted that the pivotal trial for elosulfase alfa was the double-blind, randomised, placebo-controlled, 24-week, phase 3 MOR-004 study, which investigated the efficacy and safety of enzyme replacement therapy with elosulfase alfa in 176 patients aged ≥5 years with MPS IVA (Hendriksz et al. J Inherit Metab Dis. 2014;37:979-90). The Subcommittee considered that the results of this trial demonstrated improvement in exercise tolerance at 24 weeks, but that this did not necessarily correlate to long-term benefit.

5.17. The Subcommittee considered that the primary evidence for the long-term impact of elosulfase alfa is provided by the long-term extension of the phase 1/2 MOR-002 trial (MOR-100) and the long-term extension of the pivotal phase 3 MOR-004 trial (MOR-005).

5.18. The Subcommittee noted the findings of the open-label, single-arm, phase 1/2, MOR-002 trial and its long-term extension study, MOR-100 (Hendriksz et al. Mol Genet Metab. 2018;123:479-487). The Subcommittee noted that the MOR-002 trial included a 36-week dose escalation period (elosulfase alfa, 0.1, 1, 2 mg/kg/week) and an additional 36–48-week continuation period (elosulfase alfa, 1 mg/kg/week), and that the MOR-100 study evaluated elosulfase alfa at a dose of 2 mg/kg/week for an additional 192 weeks. The Subcommittee noted that 20 individuals aged 5-18 years with MPS IVA were enrolled in MOR-002, and that 17 of these patients completed the study and were enrolled in MOR-100. The Subcommittee noted that endurance outcomes (6-minute walk test [6MWT] and 3-minute stair climb test [3MSCT]) and respiratory function were stable over the 5-year period, and that no new safety concerns were identified.

5.19. The Subcommittee considered that there were several limitations associated with MOR-002 and MOR-100, including the small sample size, the non-comparative study design, and that surgical procedures were not excluded during the study.

5.20. The Subcommittee noted a report of the impact of elosulfase alfa on activities of daily living across the domains of mobility, self-care, and caregiver assistance after 72 and 120 weeks of treatment during the 96-week, open-label extension study (MOR-005) of the pivotal 24-week MOR-004 trial (Hendriksz et al. Mol Genet Metab. 2018;123:127-134). The Subcommittee noted that at week 120, the least squares mean (standard error [SE]) change in domain scores from baseline were -0.5 (0.1) for mobility (P=0.002), -0.4 (0.1) for self-care (P=0.001), and -1.0 (0.5) for caregiver-assistance (P=0.06). The Subcommittee noted that a comparable untreated cohort of patients showed no improvement in domain scores over 2 years, and worsening in mobility and self-care.

5.21. The Subcommittee noted a post hoc sub-analysis of endurance outcomes and activities of daily living in adult patients (≥18 years) included in the MOR-005 study (Hughes et al. Orphanet J Rare Dis. 2017 May 23;12:98). The Subcommittee noted that the modified per protocol (MPP) population included 32 patients who had not undergone orthopaedic surgical procedures, and the intention to treat (ITT) population included 37 patients. The Subcommittee noted that at week 120, the least squares mean (SE) 6MWT distance increased by 34.9 (11.7) m in the MPP population and 30.5 (10.8) m in the ITT population, and the least squares mean (SE) change in 3MSCT was 6.7 (1.8) stairs/min in the MPP population and 5.9 (1.7) stairs/min in the ITT population. The Subcommittee noted that a comparable untreated cohort of patients showed no improvement in 6MWT or 3MSCT over a similar period of time. The Subcommittee noted that activities of daily living scores improved in all patients in MOR-005, whereas scores remained unchanged or worsened for individuals in the untreated cohort.

5.22. The Subcommittee considered that the evidence for elosulfase alfa for MPS IVA is of low to moderate strength and quality and considered that it is unclear whether the results observed in the clinical trials translate to meaningful long-term clinical improvement. The Subcommittee also considered that there remains significant uncertainty regarding whether elosulfase alfa will provide substantial long-term benefits in all patients with MPS IVA due to the heterogeneity of the disease. Members noted the evidence of long-term effects was limited to open-label follow-up studies that included patients who were 5 years or older at the time of starting treatment. Members considered there is no standard method to assess benefit in patients with MPS IVA.

5.23. The Subcommittee acknowledged the high health need of patients with MPS IVA, noting that the burden increases over time. The Subcommittee considered that there is currently no evidence available demonstrating that treatment with elosulfase alfa is associated with a survival benefit.

5.24. The Subcommittee noted the high proposed cost of elosulfase alfa and considered that in addition to its uncertain benefits, the cost effectiveness of elosulfase alfa is likely to be very poor.

5.25. The Subcommittee considered that elosulfase alfa is likely to benefit a sub-population of patients with MPS IVA, but that the heterogeneity of the disease creates difficulties in assessing which patient population would derive the most benefit from treatment. Members considered that the most benefit is likely to be observed in children under the age of 2 years, prior to the development of significant skeletal dysplasia, or in patients with an attenuated phenotype.

6. Nusinersen for the treatment of spinal muscular atrophy (SMA)

Application

6.1. The Subcommittee reviewed a funding application from Biogen Australia Pty Ltd for nusinersen (Spinraza) for the treatment of spinal muscular atrophy.

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

Recommendations

6.3. The Subcommittee **recommended** that nusinersen for the treatment of spinal muscular atrophy type 1 be **deferred** until longer-term follow-up analyses are published from the SHINE and/or NURTURE trials.

6.4. The Subcommittee **recommended** that nusinersen for the treatment of spinal muscular atrophy type II and IIIa be **deferred** until longer-term follow-up analyses are published from the SHINE and/or NURTURE trials.

Discussion

6.5. The Subcommittee noted that Spinal Muscular Atrophy (SMA) is a genetically determined degenerative motor neuron disorder affecting brainstem and spinal motor neurons.

6.6. The Subcommittee noted that the application was for funding of nusinersen for the treatment of paediatric patients (18 years or under) with SMA types I, II and IIIa with symptom onset before 3 years of age.

6.7. The Subcommittee considered the submissions that were provided in support of the funding application from clinicians and members of the public. The Subcommittee noted the high health need of people with SMA and their families/caregivers, and the feedback highlighting the devastating effect that SMA can have on people with SMA as well as their families, caregivers, and friends of families affected by the disorder. The Subcommittee acknowledged the many personal accounts provided in the submissions describing the significant impact SMA has on the person living with the disorder and those who support and care for those who are affected.

6.8. The Subcommittee noted that there were four main subtypes of SMA: SMA I, SMA II, SMA IIIa and SMA IIIb/IV. The Subcommittee considered the following regarding the health need of the different subtypes:

6.8.1. Infants with SMA I typically experience symptom onset within 6 months of age and that it is usually fatal by 24 months of age.

6.8.2. Children with SMA II typically experience symptom onset from 6 to 18 months with a life expectancy through until adulthood. The Subcommittee considered that approximately 50% of patients with SMA II survive up to age 40.

6.8.3. Children with SMA IIIa typically experience onset before age 3 and have a normal lifespan but are predominantly non-ambulatory.

6.8.4. Children/adults with SMA IIIb/IV typically experience onset after the age of 3, have a normal lifespan and may or may not be ambulatory.

6.9. The Subcommittee considered that the disease was more severe for those with earlier onset of symptoms and that health need was greatest for those with earlier onset of symptoms. The Subcommittee noted that SMA is incurable and in its most severe form is usually fatal, with respiratory failure being the major cause of morbidity and mortality.

6.10. The Subcommittee noted that there are no funded treatments for SMA and that supportive care includes non-pharmaceutical interventions such as nutritional support and physiotherapy to assist with respiratory (ventilation), mobility or feeding difficulties.

6.11. The Subcommittee considered that there is a high caregiver burden for patients with SMA I, II and IIIa and that modifying the phenotype from SMA I or II to SMA IIIa would likely improve this. The Subcommittee considered that, in theory, modifying the phenotype from SMA I to SMA II could also increase the burden of care, as patients with SMA II are likely to have a higher burden of care due to their living longer than currently is the case. However, the Subcommittee considered that any treatment that prolonged survival would not be seen as a burden by caregivers.

6.12. The Subcommittee noted that the reported prevalence range for SMA is from 1:13,000 to 1:77,000; and considered that it was likely to be less than 1:50,000.

6.13. The Subcommittee considered that the funding application for nusinersen met PHARMAC's principles for rare disorders (PHARMAC applied definition of a rare disorder).

6.14. The Subcommittee noted that SMA is an autosomal recessive (SMN1 gene deletion) disease, and that the incidence range was likely to be 1:8,000 to 1:11,000 live births. Based on 60,000 live births in NZ in 2017, the Subcommittee considered that this would translate to about 5 to 6 cases of SMA annually.

6.15. The Subcommittee considered that SMA I is reported in the literature to have the highest incidence of all the subtypes for SMA; however, it was noted that it was difficult to comment on what the incidence and prevalence of SMA I in NZ is as there were no patients with SMA I registered with the NZ Neuromuscular Disease (NMD) Registry in 2017 or 2018. The Subcommittee considered that this was likely due to the condition being usually fatal within the first 2 years of life. The Subcommittee considered that an anonymous new-born screening pilot programme could be useful to help identify the incidence of SMA type I in NZ. The Subcommittee considered that the Mortality Review Committee may also be able to provide some data to help with patient number estimates for SMA type I.

6.16. The Subcommittee considered that it was difficult to comment on the accuracy of the Suppliers estimates for patient numbers, due to a lack of epidemiological data for New Zealand but considered that it was possible that patient numbers had been underestimated, based on the fact that enrolment in the registry is voluntary. The Subcommittee considered that while the NZ NMD registry was helpful, there were likely to be people with non-infantile forms of SMA who have not been enrolled on the registry.

6.17. The Subcommittee considered that if there was a neonatal screening test for SMA it would be likely to increase patient number estimates, and that such data would allow more accurate NZ SMA epidemiological data.

6.18. The Subcommittee noted that nusinersen is approved by Medsafe for the treatment of 5q SMA; these mutations lead to a loss of function of the SMN1 gene, resulting in deficiency

of SMN protein. The Subcommittee noted that the SMN2 gene also produces SMN protein, but at low levels. The Subcommittee noted that nusinersen is an antisense oligonucleotide that modifies survival motor neuron 2 gene (SMN2) splicing to increase transcription of SMN protein, thus increasing the level of SMN protein in patients with SMA.

6.19. The Subcommittee noted that there are other SMA treatments currently in late-stage development.

6.20. The Subcommittee considered that the key evidence for the health benefit of nusinersen for the treatment of SMA comes from the ENDEAR (Finkel et al. N Engl J Med. 2017;377:1723-32) and CHERISH studies (Mercuri et al. N Engl J Med. 2018;378:625-35).

6.21. The Subcommittee noted the ENDEAR study was a phase 3 randomised (2:1) double-blind sham-controlled trial investigating the safety and efficacy of nusinersen for the treatment of SMA I in 122 infants.

6.21.1. The Subcommittee noted the patient group included in the trial were those aged 7 months or younger with homozygous deletion of mutation in the SMN 1 gene, and 2 copies of the SMN2 gene, who had onset of SMA symptoms at 6months or less (but not within the first week of birth) and did not have low peripheral blood oxygen saturation.

6.21.2. The Subcommittee noted that the duration of the study was planned to be 13 months; however, the study was concluded early (approximately 6 months after the last patient enrolled) due to positive results in the pre-planned interim analysis.

6.21.3. The Subcommittee noted there were two primary outcomes: motor-milestone responders according to the Hammersmith Infant Neurologic Examination (HINE) and event-free survival (time to death or permanent ventilation).

6.21.4. With regards to motor-milestone responders the Subcommittee noted that in the interim analysis 21/51 (41%) of nusinersen treated infants vs 0/27 (0%) of controls (P<0.001) had a motor-milestone response; and, in the final analysis 37/73 (51%) of nusinersen treated infants vs 0/37(0%) of controls (no P value reported) had a motor-milestone response. The Subcommittee considered the HINE to be a clinically meaningful outcome.

6.21.5. With regards to event-free survival, the Subcommittee noted that overall the risk of death or the use of permanent ventilation was 47% lower in the nusinersen group than in the control group (hazard ratio, 0.53; 95% confidence interval 0.32 to 0.89; P=0.005). The Subcommittee noted that by the end of the trial 39% of nusinersen treated patients had died or were on permanent ventilation compared with 68% of sham treated patients. The Subcommittee calculated that this translated to an Absolute Risk Reduction (ARR) of 29% with a Number Needed to Treat (NNT) of 3.4.

6.21.6. The Subcommittee considered the overall incidence of adverse events was similar in the nusinersen group and the control group (96% and 98% respectively).

6.22. The Subcommittee noted the CHERISH study was a phase 3 randomised (2:1) double blind sham-controlled trial investigating the safety and efficacy of nusinersen for the treatment of “later onset SMA” (i.e. SMAII/IIIa) in 126 children.

6.22.1. The Subcommittee noted the patients included in the trial were aged 2-12 years with genetic documentation of 5q SMA who had symptom onset after 6 months of age and were able to sit independently but unable to walk with no respiratory insufficiency.

6.22.2. The Subcommittee noted that the study was planned to be for 9 months with a follow-up period of 6 months, but that it was terminated early due positive results in favour of treatment at the pre-specified interim analysis (when all children had been enrolled for at least six months and 39 children had completed their 15-month assessment). The Subcommittee noted the primary outcome was motor-milestone response as measured by the Hammersmith Functional Motor Scale-Expanded score (HFMSE).

6.22.3. The Subcommittee noted that in the interim analysis a 4.0-point increase from baseline to month 15 was reported for the nusinersen treated group compared with a 1.9 point drop for those in the control group ($p<0.001$). The Subcommittee considered the change in HFME to be a clinically meaningful outcome for the treated group. With regards to the final analysis the Subcommittee noted that 57% of nusinersen treated patients compared to 26% of patients in the control group had an increase from baseline to month 15 in HFMSE score of at least 3.0 points ($p<0.001$).

6.22.4. The Subcommittee considered the overall incidence of adverse events was reported to be similar in the nusinersen group and the control group (93% and 100% respectively).

6.23. The Subcommittee noted that SHINE is an ongoing extension to the ENDEAR and CHERISH studies and that data from this study is yet to be published. The Subcommittee noted that this is an open label treatment study with 89 patients (65 from the nusinersen treated group and 24 from the control group of the ENDEAR study). The Subcommittee considered some preliminary results from the Supplier application that reported the median time to death or permanent ventilation as 73 weeks for the nusinersen treated group versus 22.6 weeks for the control group and that approximately 50% of the nusinersen treated group were either alive or not requiring permanent ventilation at 73 weeks. The Subcommittee considered that once the trial is published it would provide useful long-term data.

6.24. The Subcommittee noted that NURTURE is an ongoing single arm Phase II trial investigating the efficacy of nusinersen in infants with genetically diagnosed and pre-symptomatic SMA, yet to be published. The Subcommittee noted that the eligibility criteria included age $\leq$6 weeks with genetic documentation of 5q SMA and genetic documentation of 2 or 3 copies of SMN2. The Subcommittee noted that at the time of the interim analysis at 14 months (May 2018), all 25 enrolled patients were alive with no permanent ventilation and the majority of patients were achieving normal motor milestone development. The Subcommittee considered that once the trial is published it would provide useful long-term data.

6.25. The Subcommittee considered that given the two key trials (ENDEAR and CHERISH) were in two different SMA populations that it would be important to consider the health benefit that nusinersen provides to these groups separately. The Subcommittee considered that based on the ENDEAR trial there was good evidence to support a short-term benefit for an improvement in motor-milestones and a decrease in the risk of death or permanent ventilation for patients with SMA I, but no evidence to show that these benefits continue long term. The Subcommittee considered that based on the CHERISH trial there was good evidence to support a short-term benefit for improvement in motor function in patients with SMA II/IIIa, but as with the ENDEAR trial, no evidence to demonstrate that these benefits are maintained. The Subcommittee considered that based on the currently available evidence, nusinersen is not a cure for any subtypes of SMA.

6.26. Overall the Subcommittee considered that the two key trials were well conducted and that the strength and the quality of the evidence to support short term treatment effects of delaying progression of SMA was good. In addition, the Subcommittee considered that based on the available evidence, it would appear that the earlier the patient is treated the more effective the treatment is likely to be, and that treatment may shift the trajectory of the disease by modifying the phenotype e.g. shifting the disease course of SMA I to that of SMA II and shifting SMA II to that of SMA IIIa. However, the Subcommittee considered there were major concerns with regards to long term benefits for both populations, and that there is uncertainty whether the short-term benefits reported in the trials would be maintained long term.

6.27. The Subcommittee considered that there was also a lack of data to help identify which patients are most likely to respond to treatment. The Subcommittee considered that this information is important to help determine any potential criteria that could be used to ensure treatment is being targeted to those most likely to benefit and is only continuing in patients who are responding to treatment.

6.28. The Subcommittee considered that there was no available evidence at this time to support a health benefit with nusinersen treatment for patients with SMA IIIb or IV.

6.29. The Subcommittee noted that there is currently a Compassionate Access Programme in New Zealand, provided by the Supplier for patients with SMA I and considered that outcomes from this would be useful to consider along with mature data from the SHINE study as it would provide data in the New Zealand population.

6.30. The Subcommittee noted that applications for the funding of nusinersen have been reviewed by several international health technology assessment agencies. The Subcommittee noted that the UK (NICE) did not recommend funding nusinersen, that Australia (PBAC) recommended funding for the same population as described in this application, that Canada (CADTH) recommended funding only for those with SMA after the first week after birth and on or before 7 months of age and that similarly Scotland (SMC) had recommended use for symptomatic SMA I.

6.31. The Subcommittee noted nusinersen is administered by intrathecal injection which requires a dedicated hospital resource for this procedure and that intrathecal administration for paediatric patients requires specialist support, likely only available in Auckland, Christchurch and Wellington hospitals. The Subcommittee considered that

should nusinersen be funded, any patients living outside of these areas would need to travel frequently throughout the year to access treatment.

6.32. The Subcommittee noted that based on the prices proposed by the supplier, treatment with nusinersen would cost **[withheld]** per person for the first year and approximately **[withheld]** per person for each subsequent year. The Subcommittee considered there would be additional costs to the health sector associated with the specialised intrathecal administration of the drug. The Subcommittee considered that if nusinersen was funded it would be used in addition to best supportive care. The Subcommittee also considered that based on the provided evidence, and noting the unknown long-term effect of treatment, additional cost offsets due to a reduction in any of the services involved in best supportive care was uncertain. The Subcommittee considered that if nusinersen was funded it would represent a significant financial impact for uncertain long-term benefit and that based on this the cost effectiveness would be uncertain.

6.33. The Subcommittee acknowledged the high health need of people with SMA I, II and IIIa and that early evidence indicates possible health benefits from nusinersen relating to improvement in motor-milestones and a decrease in the risk of death or permanent ventilation for patients with SMA I; and, improvements in motor-milestones for patients with SMA II/IIIa. However, members considered that nusinersen was a highly expensive treatment for which the long-term benefits for both patient populations (SMA I and SMA II/IIIa) are uncertain. The Subcommittee considered it was therefore unable to make an informed recommendation until longer-term follow-up analyses are published from the SHINE and/or NURTURE trials.

7. Nitisinone for the treatment of hereditary tyrosinaemia type 1 (HT-1)

Applications

7.1. The Subcommittee reviewed two applications for the funding of nitisinone for the treatment of hereditary tyrosinaemia type 1:

7.1.1. An application from Max Health Ltd for nitisinone (Nityr) for the treatment of hereditary tyrosinaemia type 1.

7.1.2. An application from TeArai BioFarma for nitisinone (Nitisinone Dipharma) for the treatment of hereditary tyrosinaemia type 1.

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

Recommendations

7.3. The Subcommittee **recommended** that nitisinone be funded with a **high** priority for the treatment of hereditary tyrosinaemia type 1 due to high health need, lack of treatment options, and moderate evidence of benefit, subject to the following Special Authority criteria:

Initial application – (hereditary tyrosinaemia type 1) only from a metabolic physician. Approvals valid for 12 months for applications meeting the following criteria.
All of the following:

1. Patient has a confirmed diagnosis of hereditary tyrosinaemia type 1 based on detection of succinylacetone in the urine and/or blood; and
2. Patient is not suffering from any other medical conditions, including complications or sequelae of hereditary tyrosinaemia type 1, or being treated by a medicine (for a condition) that may adversely compromise the effectiveness of the drug treatment; and
3. Patient does not have another life-threatening or severe disease where the prognosis is unlikely to be influenced by therapy; and
4. Patient does not have another medical condition that might reasonably be expected to compromise a response to therapy; and
5. Nitisinone to be administered at doses no greater than 2 mg/kg body weight per day.

Renewal only from a metabolic physician or any relevant practitioner on the recommendation of 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 patient has demonstrated clinical improvement or stabilisation of the condition; and
2. Patient has not developed another life threatening or severe disease where the long term prognosis is unlikely to be influenced by therapy: and
3. Patient has not developed another medical condition that might reasonably be expected to compromise a response to therapy; and
4. Nitisinone to be administered at doses no greater than 2 mg/kg body weight per day.

Discussion

7.4. The Subcommittee noted that hereditary tyrosinaemia type 1 (HT-1) is a metabolic disorder characterised by a deficiency of fumarylacetoacetate hydrolase (FAH), the enzyme responsible for the last step in the breakdown of tyrosine. The Subcommittee noted that a deficiency in FAH results in the accumulation of toxic metabolites including fumarylacetoacetate, maloylacetoacetate, succinylacetoacetate, and succinylacetone, which results in progressive hepatic, renal, and neurological damage.

7.5. The Subcommittee noted that HT-1 typically presents in infancy with symptoms including acute liver failure, renal tubular dysfunction, coagulopathy, and porphyria-like crises. The Subcommittee noted that chronic signs of untreated disease include hepatomegaly secondary to cirrhosis, tubulopathy leading to rickets and renal failure, and neurologic crises with pain and paralysis. Patients who survive beyond infancy have an increased risk of hepatocellular carcinoma.

7.6. The Subcommittee noted a retrospective analysis of medical records of patients with HT1 in Mexico which reported an overall mortality rate of 78%, a 3-year survival rate of 10% in patients who received supportive care or nutritional treatment, and a 6-year survival rate of 60% in patients who underwent liver transplantation (Fernández-Lainez et al. Ann Hepatol. 2014;13:265-72).

7.7. The Subcommittee considered that the health need for patients with HT-1 is very high; patients are high users of health resources with significant time spent in intensive care in the first six months of life.

7.8. The Subcommittee noted that tyrosinaemia is indirectly tested through the Newborn Metabolic Screening Programme in New Zealand. Members noted that there are currently two individuals with HT-1 in the country. The Subcommittee considered that these data indicate that the prevalence of HT-1 is less than 1:50,000.

7.9. The Subcommittee noted that nitisinone is not currently approved by Medsafe, but that nitisinone (Orfadin) has received regulatory approval in Australia and the EU for the treatment of HT-1 in combination with dietary restriction of tyrosine and phenylalanine. The Subcommittee noted that Nityr has regulatory approval in the EU, US, and Australia, that Nitisinone Dipharma has regulatory approval in the UK, **[withheld pending review].** The Subcommittee noted that nitisinone is not approved for any indication other than HT-1.

7.10. The Subcommittee considered that the funding application for nitisinone met PHARMAC's principles for rare disorders (PHARMAC applied definition of a rare disorder).

7.11. The Subcommittee noted that nitisinone is the only disease-modifying treatment currently available for HT-1. The Subcommittee noted that prior to the use of nitisinone, the only treatment options were dietary restriction of phenylalanine and tyrosine, and liver transplantation. The Subcommittee noted that HT-1 is fatal if untreated.

7.12. The Subcommittee noted that nitisinone is a competitive inhibitor of 4-hydroxyphenyl-pyruvate dioxygenase (4-HPPD), an enzyme upstream of FAH in the tyrosine catabolic pathway. The Subcommittee noted that by inhibiting the normal catabolism of tyrosine earlier in the metabolic pathway, nitisinone prevents the accumulation of the toxic downstream metabolites that result in pathology in patients with HT-1.

7.13. The Subcommittee noted that nitisinone is supplied as 2 mg, 5 mg, and 10 mg tablets or capsules for oral administration. The Subcommittee noted that the recommended starting dose of nitisinone is 1 mg/kg body weight per day, which can be increased to a maximum of 2 mg/kg body weight per day as needed to achieve appropriate biochemical parameters. The Subcommittee considered nitisinone treatment is likely to be initiated in infants and that the dose of nitisinone for these patients may require part tablets.

7.14. The Subcommittee noted that applications for the funding of nitisinone for the treatment of HT-1 have been reviewed by several international health technology assessment agencies. The Subcommittee noted that Canada (CADTH) recommended that nitisinone be funded for the treatment of patients with HT-1 contingent on a price reduction of ≥74% and that Australia funds nitisinone through the Life Saving Drugs Program.

7.15. The Subcommittee considered that the primary evidence for the efficacy of nitisinone comes from two open-label, single arm studies: the NTBC study and the Québec study.

7.16. The Subcommittee noted that the regulatory approval of nitisinone internationally was based on the phase 2/3 NTBC study, which investigated the efficacy and safety of nitisinone in 207 patients with HT-1. The Subcommittee noted that these patients were compared with a historical patient population that received dietary treatment alone (n = 108). The Subcommittee noted that this study reported that patients treated with nitisinone had better survival rates than patients treated with dietary measures, particularly in the subgroup of patients treated before the age of two months; however,

the Subcommittee noted that this study has not been published and has therefore not undergone peer review.

7.17. The Subcommittee noted the primary analysis of the phase 2 Québec study which compared the outcome of 78 patients born during the first ten years that nitisinone was available in Québec with patients born in the preceding decade (Larochelle et al. 2012;107:49-54). The Subcommittee noted that three groups of patients were included in the study: patients who never received nitisinone (n = 28), patients who were first treated after 1 month of age (n = 26), and patients who were treated before 1 month of age (n = 24). The Subcommittee noted that there were no hospitalisations for acute complications of HT-1 during 5731 months of nitisinone treatment compared with 184 hospitalizations during 1312 months without treatment (P<0.001). The Subcommittee noted that 20 (71%) untreated patients underwent liver transplantation compared with 7 (26%) late-treated patients (P<0.001) and 0 early-treated patients (P<0.001). The Subcommittee noted that ten deaths occurred in patients who never received nitisinone (8 pre-transplant, 2 following transplant) and two deaths occurred in nitisinone-treated patients (following transplant)

7.18. The Subcommittee noted a systematic review which compared outcomes of HT-1 patients who received early (pre-symptomatic) nitisinone treatment to later (following symptomatic detection) nitisinone treatment (Geppert et al. Orphanet J Rare Dis. 2017;12:154). The Subcommittee noted that the review included seven articles reporting results from three cohort studies and one cross-sectional study. The Subcommittee considered that while there was consistent evidence that nitisinone was an effective treatment for HT-1, overall the study quality was considered moderate to weak with a high risk of confounding. The Subcommittee noted that post hoc analysis suggested there was an association between earlier nitisinone treatment and fewer liver transplants.

7.19. The Subcommittee noted supporting evidence for the use of nitisinone for the treatment of HT-1 was provided by a number of retrospective studies (Masurel-Paulet et al. J Inherit Metab Dis. 2008;31:81-87; Mayorandan et al. Orphanet J Rare Dis. 2014;9:107; Bartlett et al. J Inherit Metab Dis. 2014;37:745-52; Maiorana et al. Mol Genet Metab. 2014;113:188-93).

7.20. The Subcommittee considered that the relatively large differences in survival probabilities (primarily when initiated in patients younger than six months) and reduced morbidity compared with historical controls suggests that there is a clinically meaningful benefit with nitisinone treatment in patients with HT-1; however, the extent to which this would be maintained over a lifetime (approximately 80 years) is uncertain.

7.21. The Subcommittee considered that if nitisinone were to be funded, there would likely be a reduction in the number of hospitalisations and a reduction or delay in the need for liver transplantation for patients with HT-1. The Subcommittee considered that the long-term consequences for the health sector included more patients surviving into adulthood, with ongoing requirements for medical care including for the monitoring and treatment of hepatocellular carcinoma. The Subcommittee considered that the long-term neurodevelopmental impacts or potential negative effects of treatment with nitisinone are unclear.

7.22. The Subcommittee considered that the evidence available for the benefits associated with nitisinone treatment in patients with HT-1 is of low to moderate quality, but that it is

unlikely that high-quality evidence will be forthcoming. The Subcommittee considered that on the basis of the data currently available there is adequate evidence of a treatment effect in a population for whom no other disease-modifying therapy is available.

7.23. The Subcommittee noted that the applications from the suppliers were both for generic versions of nitisinone, and that only one of these suppliers had provided bioequivalence data. The Subcommittee considered that evidence of bioequivalence would be required to meet regulatory requirements; however, this would be considered by Medsafe. The Subcommittee noted the benefits of competition in the market given that generic versions of nitisinone are available and considered that PHARMAC could consider the possibility of a competitive procurement process if nitisinone were to be funded on the Pharmaceutical Schedule.

7.24. The Subcommittee noted rapid cost-utility analysis conducted by PHARMAC for nitisinone indicated that the cost-effectiveness could vary widely depending on the dose and duration of treatment, in addition to the cost. Members noted that nitisinone would likely delay or prevent the need for liver transplant and that these potential offsets were included in the analysis.

7.25. Members noted that treatment with nitisinone could stabilise patients with severe liver disease who would otherwise progress to liver transplant, and transplantation may no longer be required; however, Members considered that life-long treatment with nitisinone would then be necessary to manage HT-1.

7.26. The Subcommittee additionally noted that there are currently two patients in New Zealand who have been diagnosed with alkaptonuria; an inherited disorder resulting from a deficiency in homogentisate dioxygenase, the third enzyme in the tyrosine degradation pathway. The Subcommittee noted that patients with alkaptonuria are usually asymptomatic in childhood, but develop arthropathy, renal stones, and cardiac valve involvement later in life due to the accumulation of polymerised homogentisic acid in connective tissue.

7.27. The Subcommittee considered that while patients with alkaptonuria may theoretically benefit from treatment with nitisinone, there is insufficient evidence to support the use of nitisinone for the treatment of alkaptonuria at this time. The Subcommittee also considered that patients with alkaptonuria have a lower health need than patients with HT-1, and that nitisinone is not approved for the treatment of alkaptonuria in the US, EU, Canada, or Australia.

8. Migalastat for the treatment of Fabry disease

Application

8.1. The Subcommittee reviewed an application from Amicus Therapeutics for the funding of migalastat hydrochloride (Galafold) for the treatment of Fabry disease.

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

Recommendation

8.3. The Subcommittee **recommended** that the application for migalastat for the treatment of Fabry disease be **declined** based on insufficient evidence of long-term beneficial effects on morbidity and mortality.

Discussion

8.4. The Subcommittee noted that applications for two different agents for the treatment of Fabry disease were considered concurrently by the Rare Disorders Subcommittee at the November 2018 meeting: migalastat and agalsidase alfa.

8.5. The Subcommittee noted that PHARMAC has previously considered applications for the funding of two enzyme replacement therapies (ERTs) and migalastat for the treatment of Fabry disease. The Subcommittee noted that the Pharmacology and Therapeutics Advisory Committee (PTAC) declined applications for agalsidase beta in May 2006, February 2009, and November 2011, based on a range of issues including a lack of high quality long-term data. The Subcommittee noted that PTAC declined applications for agalsidase alfa in February 2009, and November 2011, based on insufficient evidence of benefit and unclear effects on clinically meaningful endpoints. The Subcommittee noted that PTAC considered an application for migalastat from Amicus in November 2011, noting that it was in phase 3 development at the time and was not approved for use in New Zealand. No formal recommendation regarding migalastat was made at the time.

8.6. The Subcommittee noted that Fabry disease is an X-linked lysosomal storage disorder caused by a mutation in the gene that codes for alpha-galactosidase A (α-Gal A), an enzyme responsible for the breakdown of globotriaosylceramide (GL-3). The Subcommittee noted that a deficiency in α-Gal A results in the accumulation of GL-3 in lysosomes of various cell types, leading to cellular dysfunction which triggers apoptosis, inflammation, and fibrosis.

8.7. The Subcommittee noted that the age of onset, severity of symptoms, and rate of progression of Fabry disease are highly variable depending on the degree of deficiency of α-Gal A. The Subcommittee noted that patients with no residual α-Gal A activity generally present in childhood or adolescence with symptoms including neuropathic pain, telangiectasias, angiokeratomas, gastrointestinal symptoms, corneal opacities, and renal manifestations; and that cardiac disease, cerebrovascular complications, and renal failure develop in adulthood.

8.8. The Subcommittee noted that the presentation of Fabry disease in heterozygous females can vary from asymptomatic to the full expression of classic Fabry disease historically associated with hemizygous males. The Subcommittee noted classical disease can result in early renal failure, stroke, and hypertrophic cardiomyopathy.

8.9. The Subcommittee noted that the life expectancy of untreated males with Fabry disease is reduced by 20 years compared with the general population and the life expectancy of untreated women with Fabry disease is reduced by 15 years (MacDermot et al. J Med Genet. 2001;38:750-60; MacDermot et al. J Med Genet. 2001;38:769-75).

8.10. The Subcommittee noted that Fabry disease is a chronic disease with slow deterioration expected to a point; however, the disease course is not linear and there appears to be a threshold after which deterioration is rapid. Members considered this made clinical trials difficult to design and evaluate.

8.11. The Subcommittee noted there may be a health need for others as a result of caring for patients with Fabry disease. The Subcommittee also considered that, as an inherited disorder, Fabry disease is likely to affect multiple members of the same family; this is likely to compound the burden of care for family and whānau.

8.12. The Subcommittee considered that accurate epidemiological data regarding the prevalence of Fabry disease in New Zealand is not currently available, but that extrapolation from Australian data indicates there are likely to be approximately 55 patients with Fabry disease in New Zealand. Members noted this is significantly higher than the number of patients known to have Fabry disease in New Zealand, suggesting the disease is currently under-diagnosed. The Subcommittee considered that these data indicate that the prevalence of Fabry disease is less than 1:50,000.

8.13. The Subcommittee noted that migalastat is not currently approved by Medsafe for the treatment of Fabry disease, but that the agent has received regulatory approval in Australia, Canada, the United States, and the United Kingdom. The Subcommittee noted that migalastat is not approved for any indication other than Fabry disease.

8.14. The Subcommittee considered that the funding application for migalastat met PHARMAC's principles for rare disorders (PHARMAC applied definition of a rare disorder).

8.15. The Subcommittee noted that there are currently no specific treatments for Fabry disease funded in New Zealand; and that clinical management involves treating the symptoms associated with renal impairment, vascular disease, cardiac manifestations, gastrointestinal disturbances, auditory abnormalities, and pain.

8.16. The Subcommittee noted that disease-modifying therapies that have been developed to treat Fabry disease include ERT (i.e. agalsidase beta and agalsidase alfa) and molecular chaperone therapy (i.e. migalastat). The Subcommittee noted that these agents are not currently funded in New Zealand.

8.17. The Subcommittee noted that migalastat is a pharmacological chaperone that selectively and reversibly binds with high affinity to the active site of certain mutant forms of α-Gal A. The Subcommittee noted that binding of migalastat to α-Gal A stabilizes the mutant form of the protein in the endoplasmic reticulum, facilitating proper trafficking to lysosomes and leading to the catabolism of GL-3 and related substrates.

8.18. The Subcommittee noted that migalastat is only effective in the approximately 35% to 50% of individuals with Fabry disease who have an amenable mutation.

8.19. The Subcommittee noted that the safety and efficacy of migalastat in children aged 0 to 15 years has not yet been established.

8.20. The Subcommittee noted that migalastat is administered orally at a dose of 123 mg (equivalent to migalastat hydrochloride 150 mg) every other day.

8.21. The Subcommittee noted that applications for the funding of migalastat for the treatment of Fabry disease have been reviewed by several international health technology assessment agencies. The Subcommittee noted that Canada (CADTH), Scotland (SMC), and the UK (NICE) recommend the funding of migalastat for patients with Fabry disease and an amenable mutation; and as of 1 November 2018, Australia funds migalastat for patients with Fabry disease and an amenable mutation through the Life Saving Drugs Program, provided patients are intolerant to, or have been treated with agalsidase alfa or agalsidase beta for at least 12 months.

8.22. The Subcommittee considered that the primary evidence for the efficacy of migalastat in Fabry disease comes from the phase 3 FACETS trial and the phase 3 ATTRACT trial.

8.23. The Subcommittee noted the findings of the phase 3 FACETS trial which investigated the efficacy and safety of migalastat compared with placebo in 67 patients with Fabry disease, 50 of whom were identified prior to unblinding as having an amenable mutation (Germain et al. N Engl J Med. 2016;375:545-55). The Subcommittee noted that the FACETS trials was divided into two stages: a 6-month randomised, double-blind stage, and a 6 to 12 month open-label stage followed by an additional 12 months of treatment. The Subcommittee noted that at 6 months, 13 of 32 (41%) patients who received migalastat and 9 of 32 (28%) patients who received placebo achieved a response (≥50% reduction in GL-3 inclusion per kidney interstitial capillary; *P*=0.30). The Subcommittee noted that **[withheld pending review]** of patients with amenable mutations demonstrated a greater reduction in GL-3 inclusions per kidney interstitial capillary (*P*=0.008) and lower plasma globotriaosylsphingosine levels at six months (*P*=0.003) in patients who received migalastat compared with patients who received placebo.

8.24. The Subcommittee also noted an analysis of gastrointestinal symptoms in patients with Fabry disease who had an amenable mutation in the FACETS trial (Schiffmann et al. Orphanet J Rare Dis. 2018;13:68) and an analysis of GL-3 content of podocytes of eight men with Fabry disease with amenable mutations who took part in the FACETS trial (Mauer et al. J Med Genet. 2017;54:781-786).

8.25. The Subcommittee noted the findings of the 18-month, randomised, active-controlled ATTRACT trial which investigated the efficacy of migalastat compared with ERT in patients with Fabry disease and amenable mutations who had previously received ERT (Hughes et al. J Med Genet. 2017;54:288-296). The Subcommittee noted that the ATTRACT trial was divided into two stages: an 18-month open label comparison between migalastat and ERT followed by a 12-month open-label extension with migalastat. The Subcommittee noted that migalastat and ERT had similar effects on renal function, and that left ventricular mass index decreased from baseline by -6.6 g/m^2 (95% CI -11.0 to -2.2) in patients who switched from ERT to migalastat and decreased by -2.0 g/m^2 (95% CI -11.0 to 7.0) in patients who remained on ERT.

8.26. The Subcommittee considered that if migalastat were to be funded, patients with amenable mutations would likely require fewer clinical visits and hospitalisations, and end-stage renal failure may be avoided in some patients. The Subcommittee considered that migalastat would be used in conjunction with other agents including angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and antihypertensives.

8.27. The Subcommittee noted the high proposed price for migalastat and considered that while the results of the clinical trials are promising, the evidence is limited to two trials of

short duration, one of which found no difference in response between patients who received migalastat and patients who received placebo (noting that the trial was designed to investigate response in all patients, not just those with amenable mutations). Overall, the Subcommittee considered the trial evidence for migalastat was of low quality.

8.28. The Subcommittee considered that there is less long-term and real-world data available for migalastat for Fabry disease compared with ERT. The Subcommittee also considered that ERT has the potential to be effective in all patients with Fabry disease, whereas migalastat is only effective in individuals with amenable mutations.

9. Agalsidase alfa for the treatment of Fabry disease

Application

9.1. The Subcommittee reviewed an application from Shire New Zealand Limited for the funding of agalsidase alfa (Replagal) for the treatment of Fabry disease.

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

Recommendations

9.3. The Subcommittee **recommended** 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 evidence of real-world benefit, 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. The patient 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.
2. Either:
   - 2.1. Patient has renal disease: abnormal albumin (>20 ug/min from at least 2 measurements more than 24 hours apart; male only); albumin:creatinine 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 disease caused by long-term glycosphingolipids deposition in the kidneys; or
   - 2.2. Patient has cardiac disease: left ventricular hypertrophy (determined by MRI or ECG) and/or severe arrhythmia or conduction defect; or
   - 2.3. Patient has ischaemic vascular disease: determined on objective measures; or
   - 2.4. Patient has uncontrolled chronic pain: despite use of analgesic/antiepileptic medications; and
3. Patient must not have conditions related to Fabry disease which may compromise response to enzyme replacement therapy (ERT); and

4. Patient must not have another life threatening or severe disease where the prognosis is unlikely to be influenced by ERT or might be reasonably expected to compromise a response to ERT; and
5. Agalsidase alfa to be administered at doses no greater than 0.2 mg/kg every 2 weeks.

Renewal – only from a metabolic physician or any relevant practitioner on the recommendation of 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 patient is benefitting from treatment; and
2. Patient has not had severe infusion-related adverse reactions which were not preventable by appropriate pre-medication and/or adjustment of infusion rates; and
3. Patient has not developed another life threatening or severe disease where the long term prognosis is unlikely to be influenced by ERT; and
4. Patient has not developed another medical condition that might reasonably be expected to compromise a response to ERT; and
5. Agalsidase alfa to be administered at doses no greater than 0.2 mg/kg every 2 weeks.

9.4. The Subcommittee **recommended** that PHARMAC consider running a Request for Proposal process for an enzyme replacement therapy for the treatment of Fabry disease.

Discussion

9.5. The Subcommittee noted that applications for two different agents for the treatment of Fabry disease were considered concurrently by the Rare Disorders Subcommittee at the November 2018 meeting: migalastat and agalsidase alfa.

9.6. The Subcommittee noted that PHARMAC has previously considered applications for the funding of two enzyme replacement therapies (ERTs) and migalastat for the treatment of Fabry disease. The Subcommittee noted that the Pharmacology and Therapeutics Advisory Committee (PTAC) declined applications for agalsidase beta in May 2006, February 2009, and November 2011, based on a range of issues including a lack of high quality long-term data. The Subcommittee noted that PTAC declined applications for agalsidase alfa in February 2009, and November 2011, based on insufficient evidence of benefit and unclear effects on clinically meaningful endpoints. The Subcommittee noted that PTAC considered an application from Amicus for migalastat in November 2011, noting that it was in phase 3 development at the time and was not approved for use in New Zealand. No formal recommendation regarding migalastat was made at the time.

9.7. The Subcommittee noted that Fabry disease is an X-linked lysosomal storage disorder caused by a mutation in the gene that codes for alpha-galactosidase A (α-Gal A), an enzyme responsible for the breakdown of globotriaosylceramide (GL-3). The Subcommittee noted that a deficiency in α-Gal A results in the accumulation of GL-3 in lysosomes of various cell types, leading to cellular dysfunction which triggers apoptosis, inflammation, and fibrosis.

9.8. The Subcommittee noted that the age of onset, severity of symptoms, and rate of progression of Fabry disease are highly variable depending on the degree of deficiency of α-Gal A. The Subcommittee noted that patients with no residual α-Gal A activity generally present in childhood or adolescence with symptoms including neuropathic pain, telangiectasias, angiokeratomas, gastrointestinal symptoms, corneal opacities, and renal

manifestations; and that cardiac disease, cerebrovascular complications, and renal failure develop in adulthood.

9.9. The Subcommittee noted that the presentation of Fabry disease in heterozygous females can vary from asymptomatic to the full expression of classic Fabry disease historically associated with hemizygous males. The Subcommittee noted classical disease can result in early renal failure, strokes and hypertrophic cardiomyopathy.

9.10. The Subcommittee noted that the life expectancy of untreated males with Fabry disease is reduced by 20 years compared with the general population and the life expectancy of untreated women with Fabry disease is reduced by 15 years (MacDermot et al. J Med Genet. 2001;38:750-60; MacDermot et al. J Med Genet. 2001;38:769-75).

9.11. The Subcommittee noted that Fabry disease is a chronic disease with slow deterioration expected to a point; however, the disease course is not linear and there appears to be a threshold after which deterioration is rapid. Members considered this made clinical trials difficult to design and evaluate.

9.12. The Subcommittee noted there may be a health need for other people as a result for caring for patients with Fabry disease. The Subcommittee also considered that, as an inherited disorder, Fabry disease is likely to affect multiple members of the same family; this is likely to compound the burden of care for family and whānau.

9.13. The Subcommittee noted that accurate epidemiological data regarding the prevalence of Fabry disease in New Zealand is not currently available, but that extrapolation from Australian data indicates there are likely to be approximately 55 patients with Fabry disease in New Zealand. Members noted this is significantly higher than the number of patients known to have Fabry disease in New Zealand, suggesting the disease is currently under-diagnosed. The Subcommittee considered that these data indicate that the prevalence of Fabry disease is less than 1:50,000.

9.14. The Subcommittee noted that agalsidase alfa is approved by Medsafe for long-term enzyme replacement therapy (ERT) of patients with Fabry disease. The Subcommittee noted that agalsidase alfa is not approved for any indication other than Fabry disease.

9.15. The Subcommittee considered that the funding application for agalsidase alfa met PHARMAC's principles for rare disorders (PHARMAC applied definition of a rare disorder).

9.16. The Subcommittee noted that there are currently no specific treatments for Fabry disease funded in New Zealand; clinical management involves treating the symptoms associated with renal impairment, vascular disease, cardiac manifestations, gastrointestinal disturbances, auditory abnormalities, and pain.

9.17. The Subcommittee noted that disease-modifying therapies that have been developed to treat Fabry disease include ERT (i.e. agalsidase alfa and agalsidase beta) and molecular chaperone therapy (i.e. migalastat). The Subcommittee noted that these agents are not currently funded in New Zealand.

9.18. The Subcommittee noted that agalsidase alfa is a recombinant enzyme that replaces the missing or deficient α-Gal A in patients with Fabry disease, resulting in reduced GL-3 accumulation.

9.19. The Subcommittee noted that agalsidase alfa is effective in all patients with a deficiency of α-Gal A activity.

9.20. The Subcommittee noted agalsidase alfa is administered at a dose of 0.2 mg/kg body weight every 2 weeks by intravenous infusion over a period of 40 minutes.

9.21. The Subcommittee noted that applications for the funding of agalsidase alfa for the treatment of Fabry disease have been reviewed by several international health technology assessment agencies. The Subcommittee noted that Canada (CADTH) did not recommend the funding of agalsidase alfa, that Scotland funds agalsidase alfa through the Ultra Orphan Drugs Risk Share Arrangement, and that Australia funds agalsidase alfa through the Life Saving Drugs Program.

9.22. The Subcommittee considered that the primary evidence for the efficacy of agalsidase alfa comes from the Fabry Outcome Survey which compared the outcomes of 740 patients with Fabry disease who received agalsidase alfa over 5 years with data from untreated patients from three published studies (Beck et al. Mol Genet Metab Rep. 2015;3:21-7). The Subcommittee noted that the study reported that patients treated with agalsidase alfa demonstrated slower decline in renal function and slower progression of left ventricular hypertrophy. The Subcommittee noted that patients who received agalsidase alfa had a 16% risk of a composite morbidity event after 24 months of treatment compared with 45% for untreated patients. The Subcommittee noted that the estimated median survival was 77.5 years in males who received agalsidase alfa compared with 60 years in untreated males.

9.23. The Subcommittee considered that supporting evidence for the use of agalsidase alfa for the treatment of Fabry disease is provided by a systematic review which evaluated the effectiveness and safety of ERT compared with other interventions, placebo, or no intervention for the treatment of Fabry disease (El Dib et al. Cochrane Database Syst Rev. 2016;7:CD006663). The Subcommittee noted that in the two studies comparing agalsidase alfa with placebo, there was no significant difference in GL-3 concentration in plasma but there was an improvement in pain and pain-related quality of life.

9.24. The Subcommittee noted that the conclusion of the 2016 Cochrane review stated that studies comparing ERT with placebo showed significant benefits for microvascular endothelial deposits of GL-3 and for pain-related quality of life, but found no evidence indicating whether agalsidase alfa or agalsidase beta is the superior ERT. The Subcommittee considered that this suggests that PHARMAC could consider a competitive procurement process between the two agalsidase treatments.

9.25. The Subcommittee considered that agalsidase alfa stabilises Fabry disease, preventing further deterioration. The Subcommittee therefore considered that the patients who would gain the most benefit from treatment with agalsidase alfa are those who have not yet developed end-stage organ damage; however, it was considered that identifying an optimal window for treatment would be difficult, and that there may still be cardiac and cerebrovascular benefits for patients with end-stage renal disease.

9.26. The Subcommittee considered that if agalsidase alfa were to be funded, patients may require fewer clinical visits and hospitalisations, and end-stage renal failure and the consequent need for dialysis may be avoided in some patients. The Subcommittee noted that there would be additional costs associated with agalsidase alfa infusion requirements,

and there may also be additional costs associated with monitoring plasma globotriaosylsphingosine levels.

9.27. The Subcommittee considered that agalsidase alfa would be used in conjunction with other agents including angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, antihypertensives, and statins in some patients.

9.28. The Subcommittee noted that infusion of agalsidase alfa at home may be considered for patients who have been stabilised in a controlled hospital setting and are tolerating their infusions well. Members considered that this would allow patients more control over their treatment, reduce requirements for time off work, and reduce the need for travel to a hospital setting to receive infusions.

9.29. The Subcommittee noted the high proposed cost of agalsidase alfa. The Subcommittee considered that agalsidase alfa was likely to provide a morbidity and mortality benefit in patients with Fabry disease who have a high health need and a lack of alternative treatment options. The Subcommittee emphasised that, unlike migalastat, agalsidase alfa has the potential to benefit all patients with Fabry disease, rather than just the 35% to 50% of individuals with mutations amenable to treatment with migalastat. Members considered the availability of two agalsidase products, with evidence to support these products provide similar benefit, provides competition and an opportunity for PHARMAC to manage costs and improve the cost effectiveness of the treatment of Fabry disease. Members considered PHARMAC staff should explore this further.

9.30. The Subcommittee considered that the evidence for the use of agalsidase alfa for the treatment of Fabry disease was of moderate quality, but that there was some uncertainty regarding long-term benefits. The Subcommittee considered that as a consequence, the cost effectiveness of agalsidase alfa is likely to remain poor. Members considered that the proposed Special Authority criteria should be refined to further define the patient population most likely to gain benefit from treatment with agalsidase alfa and to include stopping criteria to prevent ongoing use in patients with end-stage disease who are unlikely to receive benefit from treatment.

10. Miglustat for the treatment of Niemann-Pick disease Type C (NPC)

Application

10.1. The Subcommittee reviewed an application from TeArai BioFarma for the funding of generic miglustat for the treatment of Niemann-Pick disease Type C.

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

Recommendation

10.3. The Subcommittee **recommended** that the application for miglustat for the treatment of Niemann-Pick disease Type C be **declined** based on low quality evidence of benefit, and

concerns regarding study design including short follow-up and uncertainty regarding the applicability of endpoints to long-term outcomes.

Discussion

10.4. The Subcommittee noted that Niemann-Pick disease Type C (NPC) is a lysosomal storage disorder caused by mutations in the *NPC1* or *NPC2* genes that encode for two intracellular transporter proteins which work cooperatively to traffic intracellular lipids. The Subcommittee noted that loss of function in either protein results in accumulation of cholesterol and sphingolipids in various tissues, leading to organ dysfunction and neurological symptoms.

10.5. The Subcommittee noted that the age of onset and clinical presentation of NPC varies significantly, ranging from being fatal within the first few months of life, to a chronic progressive disorder that remains undiagnosed until adulthood.

10.6. The Subcommittee noted that the majority of patients with NPC present in middle to late childhood with symptoms of cerebellar dysfunction including clumsiness and gait problems. The Subcommittee noted that neonatal-onset NPC can also present with hepatic and pulmonary disease. The Subcommittee noted that as the disease progresses, affected individuals develop ataxia, cognitive deterioration, dystonia, dysarthria, and dysphagia. The Subcommittee noted that approximately one-third of patients develop seizures.

10.7. The Subcommittee noted that all patients with NPC die prematurely, and that the most common cause of death is aspiration pneumonia in the second or third decade of life. The Subcommittee noted that individuals with childhood-onset NPC and neurological manifestations generally deteriorate faster and die earlier than patients with later-onset disease.

10.8. The Subcommittee considered there may be a health need for other people as a result for caring for patients with NPC and there is likely to be some quality of life loss for the primary caregivers and family and whānau of people with NPC, depending on disease severity.

10.9. The Subcommittee noted that the prevalence of NPC globally is estimated to be approximately 1:100,000 population and that there is only one individual in New Zealand who is currently receiving treatment for NPC. Members considered that 1 new patient could be expected every 3 years. The Subcommittee considered that these data indicate that the prevalence of NPC is less than 1:50,000.

10.10. The Subcommittee noted that miglustat (Zavesca, Actelion Pharmaceuticals) is approved by Medsafe for the treatment of progressive neurological manifestations in adult and paediatric patients with NPC, and also for the treatment of patients with mild to moderate Type 1 Gaucher disease for whom enzyme replacement therapy is not a therapeutic option. The Subcommittee noted the TeArai generic version of miglustat is not approved by Medsafe or in Australia, **[withheld pending review]**, or Europe, and has not yet been submitted for regulatory approval. The Subcommittee noted that the prevalence of NPC and Gaucher disease globally is estimated to be 1:100,000 for each condition, and

therefore considered that the cumulative prevalence of the approved indications is less than 1:50,000.

10.11. The Subcommittee considered that the funding application for miglustat met PHARMAC's principles for rare disorders (PHARMAC applied definition of a rare disorder).

10.12. The Subcommittee noted that there are no disease-modifying agents currently funded for the treatment of NPC; treatment is palliative and varies depending on the individual's symptoms. The Subcommittee noted that best supportive care includes physical therapy, monitoring swallowing function, placement of a gastronomy tube, and medical management of seizures, dystonia, cataplexy, and bowel function.

10.13. The Subcommittee noted that miglustat acts as a competitive and reversible inhibitor of glucosylceramide synthase, the initial enzyme in a series of reactions which results in the synthesis of glycosphingolipids. The Subcommittee noted that the goal of treatment with miglustat is to reduce the rate of glycosphingolipid accumulation.

10.14. The Subcommittee noted that the recommended dose of miglustat is 200 mg three times a day for adults and adolescents with NPC and adjusted for body surface area for children under the age of 12 years with NPC. The Subcommittee noted that miglustat is administered orally.

10.15. The Subcommittee noted that applications for the funding of miglustat for the treatment of NPC have been reviewed by several international health technology assessment agencies. The Subcommittee noted Scotland (SMC) does not fund miglustat for the treatment of progressive neurological manifestations in patients with NPC, and Australia has declined to fund miglustat for NPC through the Life Saving Drugs Program due to insufficient evidence supporting the claim that miglustat was superior to placebo.

10.16. The Subcommittee noted the findings of an open-label, randomised controlled, phase 1/2 trial which investigated the effect of miglustat compared with standard of care (SoC; no study drug) on markers of NPC severity in 29 patients with NPC (Patterson et al. Lancet Neurol. 2007;6:765-72). Members noted that no placebo was used. The Subcommittee noted that at 12 months, analysis of horizontal saccadic eye movement showed a mean decrease of -0.431 (0.221) ms/deg in patients who received miglustat compared with +0.074 (0.291) in patients who received SoC (*P*=0.091). The Subcommittee also noted the findings of the 12-month open-label extension studies from this trial, published separately for the paediatric population (Patterson et al. J Child Neurol. 2010;25:300-5) and the juvenile and adult population (Wraith et al. Mol Genet Metab. 2010;99:351-7).

10.17. The Subcommittee noted the findings of a prospective open-label cohort study which investigated disease progression and response to treatment with miglustat in 20 paediatric patients with NPC (Héron et al. Orphanet J Rare Dis. 2012;7:36). The Subcommittee noted that NPC disability scores indicated stabilisation or improvement of neurological manifestations in 1/8 early-infantile, 6/8 late-infantile, and 1/3 juvenile onset patients after a median duration of treatment of 1.3, 1.0, and 1.0 years, respectively.

10.18. The Subcommittee noted the findings of a prospective open-label study which evaluated the efficacy of miglustat therapy in 25 patients with NPC (Fecarotta et al. Orphanet J Rare Dis. 2015;10:22). The Subcommittee noted that after 24 months of treatment, stabilisation or improvement in all neurological parameters was observed for the majority of the 23

patients with neurological manifestations, and that these results (with the exception of developmental delay/cognitive impairment) persisted for 48–96 months in 41% to 55% of patients.

10.19. The Subcommittee noted the findings of a prospective observational cohort study which reported on disease progression and safety in 92 patients with NPC who received continuous miglustat therapy (Patterson et al. Orphanet J Rare Dis. 2015;10:65). The Subcommittee noted that the mean miglustat exposure was 3.9 years, 59 patients (69%) were categorised as improved/stable, and the mean composite disability score was 0.37 at enrolment and 0.44 at the last follow-up visit (annual progression rate 0.038). The Subcommittee noted that chronic diarrhoea occurred in 11% of patients during the observation period.

10.20. The Subcommittee noted the findings of a retrospective observational cohort study which assessed the effect of miglustat on neurological deterioration in 66 patients with NPC (Pineda et al. Mol Genet Metab. 2009;98:243-9). The Subcommittee noted that the median miglustat exposure was 1.46 years, and that the mean annual progression rate was +0.11 score units/year from diagnosis to treatment start and -0.01 score units/year from treatment start to last clinic visit.

10.21. The Subcommittee noted a systematic literature review which included analysis of the impact of treatment with miglustat on dysphagia and other outcomes in NPC (Walterfang et al. Orphanet J Rare Dis. 2012;7:76). The Subcommittee noted that the study concluded that miglustat was reported to stabilise or improve swallowing function in a substantial proportion of patients with NPC.

10.22. The Subcommittee noted international consensus clinical management guidelines for NPC that were developed by expert physicians, geneticists, allied healthcare professionals, and patients support groups involved in the Niemann-Pick disease Registry (INDPR) project (Geberhiwot et al. Orphanet J Rare Dis. 2018;13:50). The Subcommittee noted that the guidelines recommended that all patients with a confirmed diagnosis of NPC should be considered for miglustat therapy; however, the Subcommittee noted that this recommendation was based on low-quality evidence and that 38% of experts involved in the guideline development mostly or completely disagreed with the recommendation.

10.23. The Subcommittee considered that treatment with miglustat is associated with significant gastrointestinal side effects that may be treatment-limiting, and that it is unlikely that reducing dietary disaccharide content would entirely mitigate these effects.

10.24. The Subcommittee noted the high health need of patients with NPC and considered that there would be a significant burden on caregivers looking after individuals with NPC. The Subcommittee noted that despite the lack of evidence, the availability of a possible treatment for NPC is still desirable for these families, as is often the case for diseases for which have significant impact on life expectancy.

10.25. The Subcommittee considered that the evidence for the use of miglustat for the treatment of NPC is of very low quality, provided primarily by one small phase 1/2 randomised controlled trial with supportive evidence provided by several open-label and observational cohort studies. The Subcommittee considered that the studies generally had a short follow-up and investigated surrogate endpoints for long-term outcome, such as dysphagia

and swallowing. Members noted that the studies did not compare miglustat treatment to placebo. Members considered that this made it challenging to interpret the data and, as a result, the clinical significance of any improvement in these measures remains unclear.

10.26. The Subcommittee considered that treatment with miglustat is likely to stabilise NPC and may delay progression for several years but that it is unlikely to result in significant clinical improvement. The Subcommittee also considered that there is no evidence that treatment with miglustat provides a meaningful increase in overall survival. The Subcommittee noted rapid cost-utility analysis undertaken by PHARMAC for miglustat for NPC indicated that the cost-effectiveness was likely to be very poor.

11. Miglustat for the treatment of type 1 Gaucher disease (GD1)

Application

11.1. The Subcommittee reviewed an application from TeArai BioFarma for the funding of generic miglustat for the treatment of type 1 Gaucher disease.

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

Recommendation

11.3. The Subcommittee **recommended** that the application for miglustat for the treatment of Type 1 Gaucher disease be **declined** based on low quality evidence of benefit and the adverse effect profile.

Discussion

11.4. The Subcommittee noted that Gaucher disease (GD) is an inherited lipid storage disease caused by a deficiency in glucocerebrosidase, a lysosomal hydrolase responsible for the catabolism of glucocerebroside. The Subcommittee noted that a deficiency in glucocerebrosidase results in the deposition of glucocerebroside in lysosomes of macrophages resulting in tissue damage, particularly in the liver, spleen, and bone marrow.

11.5. The Subcommittee noted that GD has traditionally been divided into three clinical subtypes: type 1 Gaucher disease (GD1) is non-neuronopathic and is the most common type of Gaucher disease, accounting for approximately 95% of cases (primarily affecting adults); type 2 Gaucher disease (GD2) is the most severe acute neuronopathic type of Gaucher disease, and is generally fatal by 2 years of age; and type 3 Gaucher disease (GD3) is also neuronopathic and characterised by sub-acute neuropathological symptoms

including seizures, cognitive impairment, and progressive encephalopathy (primarily affecting children).

11.6. The Subcommittee noted that the symptoms of GD1 can vary significantly between patients, and can include spleen and liver enlargement, anaemia, easy bruising and a tendency to bleed, and bone disease. The Subcommittee noted that the severity of GD1 varies, with some patients presenting in childhood with extensive symptoms and others remaining asymptomatic into old age.

11.7. The Subcommittee noted that symptomatic patients may die prematurely from severe anaemia, the consequences of splenectomy, severe bone disease, bleeding, infection, liver failure, or severe pulmonary disease.

11.8. The Subcommittee considered there may be a health need for other people as a result for caring for individuals with GD, and that it is likely there is some quality of life loss for the primary caregivers and family and whānau of people with Gaucher disease (depending on severity). The Subcommittee noted that individuals with GD require fortnightly infusions for enzyme replacement therapy (ERT) and that for younger patients, caregivers would likely be involved in the administration process.

11.9. The Subcommittee noted that the prevalence of GD globally is estimated to be 1:100,000 population, and that there are currently 20 patients receiving funded ERT for GD in New Zealand; 18 patients with GD1 and two patients with GD3. The Subcommittee considered that these data indicate that the prevalence of GD1 is less than 1:50,000.

11.10. The Subcommittee noted that miglustat (Zavesca, Actelion Pharmaceuticals) is approved by Medsafe for the treatment of patients with mild to moderate GD1 for whom ERT is not a therapeutic option, and for the treatment of progressive neurological manifestations in adult and paediatric patients with Niemann Pick Type C disease. The Subcommittee noted the TeArai generic version of miglustat is not approved by Medsafe or in Australia, **[withheld pending review]**, or Europe, and has not yet been submitted for regulatory approval. The Subcommittee noted that the prevalence of GD1 and Niemann Pick Type C disease globally is estimated to be 1:100,000 for each condition, and therefore considered that the cumulative prevalence of the approved indications is less than 1:50,000.

11.11. The Subcommittee considered that the funding application for miglustat met PHARMAC's principles for rare disorders (PHARMAC applied definition of a rare disorder).

11.12. The Subcommittee noted that treatment options internationally for GD include ERT (e.g., imiglucerase, taliglucerase alfa, velaglucerase alfa), substrate reduction therapy (e.g., miglustat, eliglustat), and supportive care including splenectomy.

11.13. The Subcommittee noted that in addition to supportive care, patients with GD1 and GD3 in New Zealand currently have access to two funded ERTs, imiglucerase and taliglucerase alfa, individual patient applications for which are managed by the PHARMAC Gaucher Panel. The Subcommittee noted that patients with GD2 are not eligible for funded ERTs, as the agents have little or no effect on neurological symptoms. The Subcommittee noted that in August 2017, PHARMAC released a Request for Proposals (RFP) for the supply of a first-line ERT for the treatment of Gaucher disease. The Subcommittee noted that as a result of the RFP, PHARMAC entered into an agreement with Pfizer New Zealand Limited

for the supply of taliglucerase alfa. The Subcommittee noted that as a consequence, patients are currently undergoing a change in the funded ERT for Gaucher disease, from imiglucerase to taliglucerase alfa. The Subcommittee noted that from 1 March 2019, the majority of these patients are expected to be receiving taliglucerase alfa.

11.14. The Subcommittee noted advice from the Gaucher Panel in 2016 that considered miglustat has a limited role in the treatment of GD as it has a poor side effect profile and that ERT is clinically superior.

11.15. The Subcommittee noted that ERT is administered via intravenous infusion once every two weeks.

11.16. The Subcommittee noted that miglustat is a substrate reduction therapy that acts as a competitive and reversible inhibitor of glucosylceramide synthase, the initial enzyme in a series of reactions which results in the synthesis of glycosphingolipids. The Subcommittee noted that the goal of treatment with miglustat is to reduce the rate of glycosphingolipid biosynthesis so that the amount of glycosphingolipid is reduced to a level which allows the residual activity of glucocerebrosidase to be more effective.

11.17. The Subcommittee noted that the recommended dose of miglustat for the treatment of adults with GD1 is 100 mg three times a day. The Subcommittee noted that the use of miglustat is not recommended in children and adolescents. The Subcommittee noted that miglustat is administered orally.

11.18. The Subcommittee noted that an application for the funding of miglustat was reviewed by PTAC in November 2010, at which time the Committee recommended that miglustat be funded with a low priority for the treatment of GD1 via the Gaucher panel for patients who are refractory to imiglucerase, show toxicity to imiglucerase, or are unable to comply with the imiglucerase regimen. The Subcommittee noted that miglustat remains ranked by PHARMAC as a proposal.

11.19. The Subcommittee noted that applications for the funding of miglustat for the treatment of GD have been reviewed by several international health technology assessment agencies. The Subcommittee noted Scotland (SMC) recommended that miglustat be funded in patients for whom ERT is unsuitable, and Australia funds miglustat where ERT cannot be used via the Life Saving Drug Program. The Subcommittee noted Canada (CADTH) did not recommend the funding of miglustat for the treatment of GD1 where ERT is not an option, due to a lack of adequate control groups and a focus on biochemical instead of clinical outcomes in clinical trials; insufficient evidence that miglustat has a clinically meaningful impact on haematologic and bone complications; and concerns regarding the high incidence of diarrhoea with miglustat use.

11.20. The Subcommittee noted the findings of an open-label phase 2 trial which investigated the tolerability and pharmacokinetic profile of miglustat in patients with GD1 who were clinically stable on ERT (Elstein et al. Blood 2007;110:2296-301). The Subcommittee noted that 36 patients were randomised to one of three treatment arms: miglustat alone, miglustat in combination with imiglucerase, and imiglucerase alone. The Subcommittee noted that after 6 months, there were no significant differences between treatment groups in change from baseline in organ volume, except for a reduction in liver volume in the combination group versus the imiglucerase alone group (P = 0.047). The Subcommittee noted there was no significant differences between treatment groups in mean change in

haemoglobin level and that chitotriosidase activity remained stable. The Subcommittee noted that 88% of patients receiving miglustat (n = 30) experienced diarrhoea.

11.21. The Subcommittee noted the findings of an open-label phase 2 trial which investigated the efficacy and safety of miglustat with concomitant ERT in 30 patients with GD3 (Schiffmann et al. Ann Neurol. 2008;64:514-22). The Subcommittee noted that during the initial 12 months, patients were randomly assigned 2:1 to miglustat or no miglustat treatment; this was following by an optional 12-month extension phase in which all patients received miglustat. The Subcommittee noted that organ volumes and haematological parameters remained stable between the groups, and that there was an improvement in pulmonary function and a decrease in chitotriosidase levels in patients who received miglustat compared with patients receiving ERT alone. The Subcommittee noted that 72% of patients (n = 21) experienced diarrhoea.

11.22. The Subcommittee noted the findings of a clinical study which investigated the effects of miglustat on the atherogenic profiles of 26 patients with GD1 (Puzo et al. Atherosclerosis. 2010;209:515-9). The Subcommittee noted that the study concluded that miglustat had beneficial effects on plasma lipid, lipoprotein, and CRP concentrations in patients with GD1 who were treated with miglustat for up to 36 months.

11.23. The Subcommittee noted a systematic review published by the Cochrane Collaboration which summarised all available randomised controlled study data on the efficacy and safety of ERTs and substrate reduction therapy for treatment of Gaucher disease (Shemesh et al. Cochrane Database Syst Rev. 2015;27:CD010324). The Subcommittee noted that this review reported that miglustat monotherapy appeared as effective as continued ERT for the maintenance of haematological, organ, and biomarker responses in individuals with GD1 who had previously received at least two years of treatment with ERT.

11.24. The Subcommittee considered additional evidence from a number of open-label and observational studies (Pastores et al. Clin Ther. 2007;29:1645-54, Cox et al. Orphanet J Rare Dis. 2012;7:102, Brand et al. Pharmacoepidemiol Drug Saf. 2015;24:329-33, Giraldo et al. Blood Cells Mol Dis. 2018;68:173-179, Cox et al. Lancet. 2000;355:1481-5, Elstein et al. J Inherit Metab Dis. 2004;27:757-66, Pastores et al. Clin Ther. 2005;27:1215-27, Giraldo et al. 2006;91:703-6, Giraldo et al. Haemtaologica. 2009;94:1771-5, Kuter et al. Blood Cells Mol Dis. 2013;51:116-24).

11.25. The Subcommittee considered that the health need for patients with GD1 was moderate, noting the availability of funded ERT.

11.26. The Subcommittee considered that the oral administration of miglustat was an advantage over ERT, which require infusion.

11.27. The Subcommittee considered that treatment with miglustat is associated with significant gastrointestinal side effects, and that it is unlikely that reducing dietary disaccharide content would entirely mitigate these effects. Members noted the clinical risk that some patients may prefer the weight loss effects of miglustat treatment.

11.28. The Subcommittee considered that the evidence for the use of miglustat for the treatment of GD1 is of very low quality, provided primarily by one open-label phase 2 study which demonstrated miglustat is at best non-inferior to imiglucerase in patients who were stable

on ERT and associated with significant adverse effects. The Subcommittee noted the limitations of miglustat for GD in children and adolescents under the age of 18 years. Members considered there is no evidence to support the use of miglustat in patients with refractory GD that has not responded to treatment with ERT.

11.29. The Subcommittee considered there would be limited impacts on the health system if miglustat was used to treat GD as these patients already access health resources and similar levels of monitoring and follow-up would still be required. The Subcommittee noted that some additional resources may also be required to manage adverse effects.

11.30. The Subcommittee noted the cost of miglustat and the comparable costs of ERT for GD. Members noted that taliglucerase alfa is now the first-line ERT for GD and that this agent would therefore be the relative comparator. The Subcommittee noted confidential commercial arrangements for taliglucerase alfa mean that miglustat is unlikely to be cost saving to the currently listed treatment for GD.

12. Teduglutide for the treatment of short bowel syndrome (SBS) in patients with type III intestinal failure

Application

12.1. The Subcommittee reviewed an application from Shire New Zealand Limited for the funding of teduglutide (Revestive) for the treatment of short bowel syndrome in patients with type III intestinal failure due to major intestinal resection.

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

Recommendation

12.3. The Subcommittee **recommended** that the application for teduglutide be **declined** based on the modest evidence of short-term benefit provided by treatment, lack of long-term data, and safety concerns.

Discussion

12.4. The Subcommittee noted that short bowel syndrome (SBS) is defined anatomically as having small bowel continuity of less than 200 cm, and that the condition can result from either congenital diseases or extensive surgical resection.

12.5. The Subcommittee noted that intestinal failure is defined as a reduction of gut function below the minimum necessary for the absorption of macronutrients and/or water and electrolytes, such that intravenous supplementation is required to maintain health and/or growth (Pironi et al. Clinical Nutrition. 2015;34:171-80). The Subcommittee noted that SBS is the most common cause of intestinal failure.

12.6. The Subcommittee noted that intestinal failure is classified as type I, II, or III based on onset, metabolic stability and expected outcome criteria. The Subcommittee noted that type III intestinal failure is defined as a chronic condition in metabolically stable patients that requires intravenous supplementation over the course of months to years and may be reversible or irreversible.

12.7. The Subcommittee noted that the application for the funding of teduglutide was specific to SBS in patients with type III intestinal failure due to major intestinal resection. The Subcommittee considered that there are a number of underlying conditions that can result in major intestinal resection, including Crohn's disease, trauma, malignancy, or mesenteric ischemia. The Subcommittee considered that as a consequence, the population of patients with SBS and type III intestinal failure due to resection is highly heterogeneous with patients having variable remaining bowel anatomy, comorbidities, and management requirements.

12.8. The Subcommittee noted that the general symptoms of SBS and intestinal failure include diarrhoea, dehydration, electrolyte disturbances, and malnutrition.

12.9. The Subcommittee noted that the current standard of care for patients with SBS and type III intestinal failure includes enteral and parenteral support, dietary interventions, oral rehydration solutions, anti-motility agents, and anti-secretory agents. The Subcommittee noted that these treatments are individualised depending on the functional capacity of the remaining bowel, the specific nutritional requirements of the patient, and individual preference.

12.10. The Subcommittee noted that patients requiring long-term parenteral support are generally taught to self-administer nutrition and intravenous fluids at home via a central venous catheter (home parenteral nutrition [HPN]).

12.11. The Subcommittee noted that parenteral support is associated with a number of complications including catheter-related infections, thrombosis, occlusions, and breakages; hepatic and biliary complications; renal dysfunction; and metabolic bone disease.

12.12. The Subcommittee noted that survival for patients with SBS and intestinal failure who are receiving parenteral support varies depending on the age of the patient, the severity of underlying disease, and the duration of parenteral nutrition received.

12.13. The Subcommittee noted a retrospective cohort study which reported a 5-year survival of 64% among patients with chronic intestinal failure who were receiving home parenteral nutrition (Joly et al. Clin Nutr. 2018;37:1415-22).

12.14. The Subcommittee noted that patients receiving HPN report reduced quality of life due to decreased physical functioning, decreased social functioning, fear of adverse events, impaired sleep, and daytime fatigue.

12.15. The Subcommittee considered that there would be a health need for others as a result of caring for patients with SBS with intestinal failure, and that there is likely to be some quality of life loss for primary caregivers, family, and whānau, particularly considering the requirements associated with HPN.

12.16. The Subcommittee noted that data from the New Zealand Intestinal Failure service suggests that there are 250 patients receiving long-term (>20 day) parenteral nutrition in New Zealand, and that approximately 40 of these patients have Type III intestinal failure. Members noted that it was not clear whether this data included paediatric patients. The Subcommittee considered that while these data indicate that the prevalence of SBS with type III intestinal failure due to major intestinal resection is likely to be less than 1:50,000, there remains significant uncertainty regarding whether the use of teduglutide could be limited to this population. Members considered that teduglutide could potentially benefit a large proportion of patients receiving parenteral nutrition, and that if all patients with SBS were included, the size of the population would no longer fit PHARMAC's criteria for a rare disorder.

12.17. The Subcommittee noted that teduglutide is not currently approved by Medsafe; however, it was noted that an application for the registration of teduglutide was accepted by Medsafe in August 2017, and additional evaluation was started in July 2018. The Subcommittee noted that teduglutide has received regulatory approval for the treatment of SBS for patients who are dependent on parenteral support in Australia, the US, Canada, and the EU. The Subcommittee noted that teduglutide is not indicated for the treatment of any other condition.

12.18. The Subcommittee considered that the funding application for teduglutide met PHARMAC's principles for rare disorders (PHARMAC applied definition of a rare disorder).

12.19. The Subcommittee noted that teduglutide is a long-acting analogue of naturally-occurring human glucagon-like peptide-2 (GLP-2), a peptide secreted by L-cell of the distal intestine. The Subcommittee noted that teduglutide binds to and activates GLP-2–receptors, resulting in the local release of multiple mediators with intestinotrophic effects.

12.20. The Subcommittee noted that the recommended dose of teduglutide is 0.05 mg/kg/day administered as a subcutaneous injection. The Subcommittee noted that teduglutide is supplied as single use vials containing 5 mg teduglutide powder with prefilled syringes containing 0.5 mL sterile water for reconstitution. The Subcommittee noted that any remaining unused portion is discarded.

12.21. The Subcommittee noted that applications for the funding of teduglutide for the treatment of SBS have been reviewed by several international health technology assessment agencies. The Subcommittee noted that Canada (CADTH) recommended that teduglutide be reimbursed for adult patients with SBS and that Scotland (SMC) accepted teduglutide for restricted use in patients one year and above with SBS. Members noted that these indications are broader than the population described within the application. The Subcommittee noted that Australia (PBAC) did not recommend the funding of teduglutide for the treatment of type III (chronic) intestinal failure associated with SBS.

12.22. The Subcommittee considered that the primary evidence for the use of teduglutide for the treatment of SBS with intestinal failure is provided by the double-blind, randomised, placebo-controlled, phase 3 STEPS trial, which investigated whether treatment with teduglutide 0.05 mg/kg/day reduced parenteral support in 86 adults with SBS and intestinal failure (Jeppesen et al. Gastroenterology. 2012;143:1473-1481). The Subcommittee noted that the primary endpoint was the proportion of patients who demonstrated a response at week 20 and maintained that response at week 24, with response defined as achieving ≥20% reduction in parenteral support volume from

baseline. The Subcommittee noted that 27/43 (63%) patients who received teduglutide were considered responders compared with 13/43 (30%) patients who receive placebo (*P* = 0.002). The Subcommittee noted that the number of patients experiencing adverse events was comparable between the treatment arms, and that the most commonly occurring treatment-emergent adverse events (TEAEs) in patients who received teduglutide were abdominal pain, nausea, gastrointestinal stroma complication, and abdominal distension.

12.23. The Subcommittee noted the quality of life analysis from the STEPS trial, which reported that a reduction in parenteral support was associated with quality of life improvements (Jeppesen et al. Clin Nutr. 2013;32:713-21). The Subcommittee noted that the publication also reported that treatment with teduglutide resulted in improvement in quality of life scores but that this change was not significant compared with placebo.

12.24. The Subcommittee noted the two-year open-label extension of the STEPS trial, STEPS-2 (Schwartz et al. Clin Transl Gastroenterol. 2016;7:e142). The Subcommittee noted that 65 patients completed STEPS-2; the most common TEAEs were abdominal pain (34%), catheter sepsis (28%), and decreased weight (25%); and mean parenteral support volumes reduced from baseline by 7.6 L/week (66%) in patients who received teduglutide followed by teduglutide, 3.1 L/week (28%) in patients who received placebo followed by teduglutide, and 4.0 L/week (39%) in patients who received no treatment followed by teduglutide.

12.25. The Subcommittee considered additional evidence provided by STEPS-3, an additional 1-year open-label extensions of the STEPS-2 trial (poster only, Iyer et al. Clinical Nutrition. 2014;33:S167-S168 [PP102-MON]); Study 004, an additional phase 3 trial which investigated the ability of teduglutide at doses of 0.10 mg/kg/day or 0.05 mg/kg/day to reduce parenteral support in patients with SBS with intestinal failure (Jeppesen et al. Gut. 2011;60:902-14); and Study 005, a 28-week double-blind extension trial of Study 004 (O'Keefe et al. Clin Gastroenterol Hepatol. 2013;11:815-23).

12.26. The Subcommittee noted evidence regarding the use of teduglutide in a paediatric population provided by a 12-week open-label study which included 42 patients between the ages of 1 and 17 years with SBS and intestinal failure (Carter et al. J Pediatr. 2017;181:102-111). The Subcommittee noted that teduglutide was well tolerated within the study and that treatment was associated with a trend towards a reduction in the requirement for parenteral support; however, the Subcommittee considered that the results were not conclusive of benefit.

12.27. The Subcommittee considered that there is no evidence available at this time demonstrating a benefit of treatment with teduglutide in individuals with SBS due to congenital abnormalities.

12.28. The Subcommittee considered that a reduction in requirement for parenteral support has the potential to result in improvements in quality of life beyond the patient to include family and whānau.

12.29. The Subcommittee considered that there is unlikely to be any concerns regarding the daily subcutaneous administration of teduglutide, as patients with SBS and intestinal failure are in regular contact with the health care system and routinely self-administer HPN.

12.30. The Subcommittee noted important safety information mentioned on the manufacturer's website including the potential for malignancy, polyps and bowel obstruction, and stoma dysfunction in relation to teduglutide use.

12.31. The Subcommittee considered that there were some issues with the economic model provided by the supplier, in particular regarding the assumption that patients receiving standard of care demonstrated no improvement when 30% of patients in the placebo arm of the STEPS trial achieved a response. The Subcommittee also noted that the economic model was limited to a time horizon of 20 years, which is not equivalent to a life-time horizon.

12.32. The Subcommittee considered that the use of teduglutide may reduce the need for parenteral support for some patients with SBS and intestinal failure. The Subcommittee noted that parenteral support is associated with significant financial and resource costs to the health system, in addition to negatively affecting patient quality of life and productivity. Members noted there could be some cost offsets from reduced parental nutrition; however, patients would also likely require ongoing treatment with teduglutide.

12.33. The Subcommittee noted the number of patients in the applicant's analysis and considered there is uncertainty regarding the expected uptake of teduglutide.

12.34. The Subcommittee considered that overall, there was moderate quality evidence demonstrating that treatment with teduglutide resulted in a modest short-term benefit in patients with SBS and type III intestinal failure, but that it remains unclear whether treatment with teduglutide results in an improvement in long-term outcomes or quality of life. Members noted that it is unclear whether there is a benefit of treatment with teduglutide for children with SBS and type III intestinal failure. The Subcommittee also considered that there were significant safety concerns associated with the long-term use of teduglutide that required further study.

12.35. The Subcommittee considered that the proposed cost of teduglutide was very high considering treatment provided only a modest benefit which may not be clinically meaningful for patients with SBS and type III intestinal failure.

12.36. The Subcommittee considered that further evidence demonstrating safety and a long-term reduced need for parenteral nutrition and consequent improvement in quality of life data would be needed before teduglutide could be reconsidered for funding.

13. Alglucosidase alfa for the treatment of Late-onset Pompe disease (LOPD)

Application

13.1. The Subcommittee reviewed an application from Sanofi Genzyme for the funding of alglucosidase alfa (Myozyme) for the treatment of late-onset Pompe disease.

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

Recommendation

13.3. The Subcommittee **recommended** that the application for alglucosidase alfa for the treatment of late onset Pompe disease be **declined** 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.

13.4. The Subcommittee would welcome an application for alglucosidase alfa targeting treatment to those individuals considered to have juvenile-onset Pompe disease.

Discussion

13.5. The Subcommittee noted that PTAC had reviewed the evidence regarding the use of alglucosidase alfa for the long-term treatment of late-onset Pompe disease (LOPD) on a number of occasions between 2009 and 2017. The Subcommittee noted that PTAC had previously recommended alglucosidase alfa for LOPD be declined; PTAC had noted the significant unmet health need faced by patients with LOPD but considered that overall the evidence available did not demonstrate a clinically significant benefit from treatment with alglucosidase alfa. PTAC considered that it is extremely difficult to determine which patients could potentially experience clinical improvement with enzyme replacement therapy (ERT) with alglucosidase alfa from currently available clinical data.

13.6. The Subcommittee noted that Pompe disease is a rare lysosomal storage disease caused by a deficiency of the lysosomal enzyme acid alfa-glucosidase (GAA), which results in the accumulation of glycogen in almost all tissues but predominantly skeletal muscle. The Subcommittee noted that LOPD is a multisystem disorder that typically manifests as limb-girdle muscle weakness, respiratory symptoms, and progression to respiratory insufficiency due to diaphragmatic and intercostal muscle weakness.

13.7. The Subcommittee noted a 2005 survey of Dutch patients (Hagemans et al. Brain 2005;128:671-7) which reported a mean age of symptom-onset of 28 years (±14.3 years), and that 18% of patients surveyed had symptoms before 12 years of age. Members noted that generally, patients experience loss of ambulation in their mid-forties.

13.8. The Subcommittee noted that life expectancy is reduced in patients with Pompe Disease. The Subcommittee noted that the median survival after diagnosis of 268 adult patients without ERT in the Pompe Register between 2002 and 2009 was 27 years, and that the estimated 5-year survival was 95% (Güngör et al. Orphanet J of Rare Dis. 2011;5:34). The Subcommittee noted that the estimated survival dropped to 83%, 65% and 40% at years 10, 20, and 30, respectively; and that the five-year survival for patients without a wheelchair or respiratory support was 95% compared with 74% in patients who were wheelchair-bound and required respiratory support.

13.9. The Subcommittee noted that the rate of progression and sequence of respiratory and skeletal involvement in LOPD is highly variable and appears to be related to disease duration rather than age.

13.10. The Subcommittee noted that there are two subtypes of Pompe disease: infantile-onset, which is diagnosed in the first year of life and causes serious disease including cardiomyopathy; and LOPD, where diagnosis is made at over one year of age or under

one but without cardiomyopathy. Members noted that LOPD can present as early as the first decade of childhood, or as late as the sixth decade of adulthood, and that juvenile-onset Pompe disease is a subset of LOPD where onset occurs later in childhood or adolescence. Members noted that alglucosidase alfa has been listed on the Pharmaceutical Schedule for the treatment of Infantile-onset Pompe disease since December 2016 with criteria for patients up to 24 months of age; however, there are currently no patients on treatment.

13.11. The Subcommittee noted that there are no specific treatments for LOPD funded in New Zealand; clinical management involves treating the symptoms associated with limb-girdle muscle weakness, respiratory symptoms, and progression to respiratory insufficiency. The Subcommittee noted that this often requires a multidisciplinary approach due to the broad spectrum of clinical manifestations associated with LOPD. The Subcommittee noted this could include clinical management and rehabilitation to preserve motor function, lung function and minimise secondary complications, nutritional support, and surgical intervention to manage contractures.

13.12. The Subcommittee acknowledged the high health need of patients with LOPD, noting that the burden increases over time. Members noted that LOPD can have a high emotional and psychological impact on families and puts a significant burden on caregivers.

13.13. The Subcommittee considered that epidemiological data regarding the prevalence of LOPD disease in New Zealand indicates that there are currently nine patients in New Zealand with diagnosed LOPD. The Subcommittee noted that three of the diagnosed patients are of Māori ethnicity. Members noted that a number of patients with LOPD in New Zealand currently receive ERT as compassionate supply or via a clinical trial. The Subcommittee considered that these data indicate that the prevalence of Pompe disease is less than 1:50,000.

13.14. The Subcommittee noted that alglucosidase alfa is approved by Medsafe for the long-term treatment of Pompe disease in children and adults of all ages. The Subcommittee noted that alglucosidase alfa is not indicated for the treatment of any other condition.

13.15. The Subcommittee considered that the application for the funding of alglucosidase alfa met PHARMAC's principles for rare disorders (PHARMAC applied definition of a rare disorder).

13.16. The Subcommittee noted that the recommended dosage of alglucosidase alfa is 20 mg/kg of body weight administered via infusion every two weeks over a period of four hours.

13.17. The Subcommittee noted that applications for the funding of alglucosidase alfa for the treatment of LOPD have been reviewed by several international health technology assessment agencies. The Subcommittee noted that Canada (CADTH), Scotland (SMC), and UK (AWMSG) did not recommend the funding of alglucosidase alfa for LOPD, that Australia funds alglucosidase alfa through the Life Saving Drugs Program, and that the UK funds alglucosidase alfa for the treatment of LOPD through Orphan Drug Schemes.

13.18. The Subcommittee noted that previous PTAC considerations of the evidence were extensive and covered available data up to the end of 2016. The Subcommittee considered key evidence identified by the supplier that had previously considered by

PTAC, as well as new evidence that has been published since the Committee's 2016 review.

13.19. The Subcommittee noted one systematic review and one cohort study that have been published since 2016.

13.20. The Subcommittee noted a publication of the 2017 European Consensus for starting and stopping ERT in adult patients with Pompe disease, which included a systematic review investigating the efficacy of ERT in adults with Pompe disease (van der Ploeg et al. Eur J Neurol. 2017;24(6):768-e31). The Subcommittee noted that data from one clinical trial and 43 observational studies, covering a total of 586 individual adult patients, provided evidence of a beneficial effect of ERT at group level; at the individual patient level, the response to treatment varied, but the factors associated with a patient's response to ERT were rarely described. The Subcommittee considered that survival benefit was not explored in sufficient detail in the analysis. Members considered that the publication provided useful information regarding starting and stopping criteria for ERT.

13.21. The Subcommittee noted a prospective cohort study conducted in the Netherlands which included 102 adult patients with Pompe disease (Kuperus et al. Neurology. 2017 Dec 5;89(23):2365-73). The Subcommittee noted that the median follow-up duration was 6.1 years (range 0.4 to 7.9 years), of which 5.0 years (range 0.2 to 7.3 years) were during ERT. The Subcommittee noted that the authors concluded that treated patients had better muscle strength, activity levels, pulmonary function, and improved daily life activities compared to what would have been expected for their untreated disease course. The Subcommittee noted that the largest increase was seen during the first two to three years of treatment. Members questioned whether this indicated that the benefit of treatment may peak after the first few years of treatment and then decline.

13.22. The Subcommittee noted a systematic review and meta-analysis first considered by PTAC as an unpublished article in 2016 that was subsequently published in 2017 (Schoser et al. Neurology 2017;264:621-30). The Subcommittee noted that this meta-analysis examined the effect of ERT on survival, motor, and respiratory function; and assessed the effect of treatment on wheelchair use and ventilator status (although it did not draw any conclusions regarding wheelchair use and ventilator status). The Subcommittee noted that the meta-analysis used a variety of synthesis methods to evaluate data from 19 studies (438 patients) which had investigated the effect of alglucosidase alfa for the treatment of LOPD. Members noted that the analysis concluded that the risk of mortality in treated patients was reduced to close to one fifth of that experienced by untreated patients (a rate ratio of 0.21; 95% CI 0.11 to 0.41), and varying benefit was described across all other clinical outcomes. The Subcommittee considered the effect size appeared significant; however, the clinical significance of this effect was unclear. Members noted some concerns regarding the quality of the systematic review given the heterogeneity of the studies included and uncertainty regarding how the results were calculated. Members noted that PTAC had noted similar concerns in its 2016 review of the unpublished data.

13.23. The Subcommittee noted the results of a prospective survey which reported that ERT reduced the risk of wheelchair dependency in adult Pompe patients (van der Meijden et al. Orphanet J Rare Diseases 2018;13:82-4). The Subcommittee noted that data were collected as part of a prospective international survey, the IPA/Erasmus MC Pompe survey, which was conducted annually between 2002 and 2016. The Subcommittee noted the inclusion criteria for analysing the risk of wheelchair use were met by 189 patients

(median age 47 years; range 18 to 75). The Subcommittee noted that during follow-up, 126 (67%) patients started ERT. The Subcommittee noted that over 1120 person-years of follow-up (median 5 years), 46 individuals became wheelchair dependent, 16 of whom used ERT; after adjustment for disease duration, sex and country, ERT was reported to reduce the risk of wheelchair use (HR 0.36; 95% CI 0.17 to 0.75).

13.24. The Subcommittee noted the findings of a French Pompe Registry data which included 12 patients with severe respiratory failure and permanent wheelchair use at the time of ERT initiation (Papadopoulos C et al. Mol Genet Metab 2017;122:80-5). The Subcommittee noted that during the observational period no adverse reaction to ERT was recorded; five patients (41.67%) died; three decreased their ventilation time by 30, 60 and 90 min, respectively; and two increased their assisted walking distance by 80 and 20 metres, respectively. The Subcommittee considered that the use of ERT in the late stages of LOPD would provide very limited benefit.

13.25. Members noted a recent Dutch study investigating the cost-effectiveness of ERT compared to supportive treatment in adult patients with Pompe disease (Kanters et al. Orphanet J Rare Diseases 2017;12:179-91). The Subcommittee noted that the cost-effectiveness model reported substantial survival gains from ERT; and that despite these substantial gains, ERT was not cost-effective in the treatment of adult Pompe disease because of the high cost of treatment.

13.26. While recognising the challenges of generating high-quality data for rare conditions such as Pompe disease, the Subcommittee considered that the observational data set for LOPD did not provide a sufficient basis to demonstrate substantial life extension and there remains significant uncertainty regarding treatment effect. Members considered the clinical benefits with regards to ambulation and pulmonary function are modest.

13.27. The Subcommittee noted the high proposed cost of alglucosidase alfa and considered that with uncertain benefits, the cost effectiveness of ERT for all patients with LOPD is very poor.

13.28. The Subcommittee noted that they would be interested in considering a re-submission from the supplier for alglucosidase alfa targeted to a sub-group of patients with LOPD in younger patients who could be considered to have juvenile-onset Pompe disease, as it considered this group would likely gain more benefit from treatment. Members noted there are currently no patients in New Zealand who would meet this definition.

13.29. The Subcommittee noted there were several new treatments in the development pipeline that may provide alternative treatments to consider in the future.

14. Ivacaftor the treatment of Cystic Fibrosis

Application

14.1. The Subcommittee reviewed an application from Vertex Pharmaceuticals for the funding of ivacaftor (Kalydeco) for the treatment of cystic fibrosis in patients with a G551D mutation.

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

Recommendation

14.3. The Subcommittee **recommended** that ivacaftor be funded with a **medium** priority for the treatment of cystic fibrosis in patients with a G551D mutation based on high health need, a lack of disease-modifying treatment options, and moderate quality evidence of a health benefit noting the limited availability of long-term data, subject to the following Special Authority criteria:

Initial application – only from a specialist respiratory physician or paediatrician with experience and expertise in the management of cystic fibrosis. Approvals valid for 6 months for applications meeting the following criteria:
All of the following:

1. Patient has been diagnosed with cystic fibrosis; and
2. Either:
    2.1. Patient must have G551D mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene on at least 1 allele; or
    2.2. Patient must have other gating (class III) mutation in the CFTR gene on at least 1 allele; and
3. Patient must have a sweat chloride value of at least 60 mmol/L by quantitative pilocarpine iontophoresis; and
4. Patient must not receive more than 24 weeks of treatment under this restriction; and
5. Treatment with ivacaftor must be given concomitantly with standard therapy for this condition; and
6. Patient must not have an acute upper or lower respiratory infection, pulmonary exacerbation, or changes in therapy (including antibiotics) for pulmonary disease in the last 4 weeks prior to commencing treatment with ivacaftor.

Renewal – only from a specialist respiratory physician or paediatrician with experience and expertise in the management of cystic fibrosis. Approvals valid for 6 months for application meeting the following criteria:

1. The treatment remains appropriate and the patient is benefitting from treatment as demonstrated by XXX (to be completed following advice from physicians who specialised in treating cystic fibrosis).

Discussion

14.4. The Subcommittee noted that PHARMAC has previously considered applications for the funding of ivacaftor for the treatment of cystic fibrosis in patients with G551D gene mutation on several occasions. The Subcommittee noted that in April 2014, the Respiratory Subcommittee deferred making a recommendation on ivacaftor until further clinical trial data became available evaluating ivacaftor in combination with lumacaftor, and until PHARMAC had completed further cost utility analysis. The Subcommittee noted that in May 2014, the Pharmacology and Therapeutics Advisory Committee (PTAC) deferred making a recommendation on ivacaftor for the same reasons. The Subcommittee noted that PTAC reviewed the cost effectiveness of ivacaftor in May 2015, and recommended that the application for ivacaftor be declined based on prohibitive cost and because the clinical trial results for the combination treatment had not yet been published.

14.5. The Subcommittee noted a number of submissions recently provided to PHARMAC from clinicians and members of the public in support of the funding application. The Subcommittee noted the high health need of people with cystic fibrosis and their families/caregivers, and the feedback highlighting the effect that cystic fibrosis can have on people with the disease, as well as their families, caregivers, and friends.

14.6. The Subcommittee noted that cystic fibrosis is an autosomal recessive disease caused by a mutation in the gene that encodes for the cystic fibrosis transmembrane conductance regulator (CFTR) protein, an ATP-gated anion channel which regulates the movement of ions across epithelial membranes. The Subcommittee noted that in the lungs, dysfunction in CFTR results in the production of thick, viscous secretions which compromise mucociliary clearance. The Subcommittee noted that other organs are also affected by dysfunction in CFTR, including the pancreas, liver, intestine, and reproductive tract.

14.7. The Subcommittee noted that cystic fibrosis is characterised by persistent lung infection, progressive loss of lung function, and pancreatic insufficiency resulting in malabsorption and malnutrition.

14.8. The Subcommittee noted that the severity of cystic fibrosis varies significantly from person to person depending on the degree of dysfunction in CFTR and the degree of lung involvement; however, the Subcommittee noted that deterioration is inevitable, resulting in progressive organ damage and eventually death. The Subcommittee noted that the life expectancy of individuals with cystic fibrosis is approximately 40 years.

14.9. The Subcommittee noted that the quality of life of individuals with cystic fibrosis is significantly impacted by the symptoms of disease, the intensive treatment regimens, and the frequent need for hospitalisation due to pulmonary exacerbation.

14.10. The Subcommittee noted that there is likely to be a health need for others as a result of caring for patients with cystic fibrosis. The Subcommittee noted that much of the burden of caring for a child with cystic fibrosis falls on the family and whānau, which imposes a high emotional and psychological burden due to the intensive and time-consuming treatment regimens, costs, and frequent need for medical intervention.

14.11. The Subcommittee noted that more than 1900 mutations in the CFTR gene have been identified, and that these mutations are categorised into one of five classes depending on the impact they have on the synthesis, processing, or function of the CFTR gene. The

Subcommittee noted that the G551D mutation is a gating or Class III mutation which results in the CFTR protein being present on the apical cell membrane but with greatly reduced chloride transport capability. The Subcommittee noted that approximately 4% of patients with cystic fibrosis worldwide have a G551D mutation on at least one allele.

14.12. The Subcommittee noted that the Port CFNZ data registry report from 2014 indicated that there are 443 individuals with cystic fibrosis in New Zealand, and that 30 of these individuals have the G551D mutation. Members considered that currently other Class III (gating) mutations in the CFTR gene are rare and would be unlikely to significantly affect the prevalence in New Zealand. The Subcommittee considered that these data indicate that the cumulative prevalence of cystic fibrosis due to G551D mutation or other Class III (gating) mutations is likely to be less than 1:50,000 and therefore this subgroup of patients with cystic fibrosis could be considered rare.

14.13. The Subcommittee noted that ivacaftor is approved by Medsafe for the treatment of cystic fibrosis in patients aged 6 years and older who have a G551D or other gating (Class III) mutation in the CFTR gene. The Subcommittee noted that ivacaftor is not approved in New Zealand for any indication other than that stated above, including cystic fibrosis due to other mutations. The Subcommittee noted ivacaftor has different approved indications in other jurisdictions such as the US and Europe. The Subcommittee considered that the ivacaftor funding application appeared to meet PHARMAC's principles for rare disorders based on current information (PHARMAC applied definition of a rare disorder); however, at this time there is uncertainty regarding the use of ivacaftor in combination with other agents. Members noted that the efficacy of ivacaftor monotherapy has not been reported in other forms of cystic fibrosis to date. The Subcommittee considered that cystic fibrosis is not a rare disorder based on the PHARMAC definition, and therefore ivacaftor in combination with other agents, or any other treatments that were approved for use in a wider CF population would not meet PHARMAC's principles for rare disorders and would therefore be considered by PHARMAC through the usual funding assessment process, following Medsafe regulatory approval.

14.14. The Subcommittee noted that there are currently no disease-modifying therapies funded for the treatment of cystic fibrosis in New Zealand; treatment is limited to symptomatic therapies that address disease manifestations. The Subcommittee noted that the aim of treatment is to maintain lung function by controlling respiratory infections and clearing the airway of mucus, and to provide nutritional support. The Subcommittee noted that current treatments include inhaled hypertonic saline, dornase alfa (via the Cystic Fibrosis Advisory Panel Special Authority), inhaled bronchodilators, oral and inhaled steroids, oral and/or nebulised antibiotics, digestive enzymes, vitamin supplements, and regular physiotherapy.

14.15. The Subcommittee noted that for individuals with end-stage lung disease, lung transplantation is an option; however, members noted that lung transplants for cystic fibrosis are relatively uncommon in New Zealand at this time.

14.16. The Subcommittee noted that ivacaftor is a selective potentiator of CFTR; in vitro ivacaftor increases the open probability of the CFTR channel gate to enhance chloride transport. The Subcommittee noted that the exact mechanism that results in ivacaftor prolonging the gating activity of some mutant CFTR forms has not been completely elucidated.

14.17. The Subcommittee noted that the recommended dose of ivacaftor is 150 mg taken orally every 12 hours (300 mg total daily dose; supplied as film-coated tablets). The Subcommittee noted that 50 mg and 75 mg sachets of ivacaftor granules are available in some countries but are not currently approved by Medsafe or available in New Zealand. The Subcommittee considered that there may be issues with how ivacaftor can be prepared for paediatric use if only film-coated tablets are available.

14.18. The Subcommittee noted that applications for the funding of ivacaftor for the treatment of cystic fibrosis have been reviewed by several international health technology assessment agencies. The Subcommittee noted that Australia funds ivacaftor for the treatment of cystic fibrosis in patients aged 6 years and older with a G551D or other gating (class III) mutation in CFTR, the UK funds ivacaftor for the treatment of cystic fibrosis in patients aged 6 years and older with at least one copy of an appropriate gating mutation, and Canada funds ivacaftor for patients aged 6 years and older with G551D or other gating mutations and in patients 18 years and older with R117H mutations (Class IV). The Subcommittee noted that ivacaftor is not recommended for use within NHS Scotland (SMC).

14.19. The Subcommittee considered that the primary evidence for the efficacy and safety of ivacaftor for the treatment of patients with cystic fibrosis with a G551D mutation is provided by three phase 3 clinical trials (STRIVE, EVISION, and PERSIST) and one observational, post-approval safety study.

14.20. The Subcommittee noted the findings of the randomised, double-blind, placebo-controlled, phase 3 STRIVE trial, which evaluated ivacaftor in 167 patients aged 12 years or older with cystic fibrosis and at least one G551D mutation (Ramsey et al NEJM 2011;365:1663-72). The Subcommittee noted that after 24 weeks of treatment, there was an increase from baseline of 10.4 percentage points in the percent predicted FEV_1 in patients who received ivacaftor compared with a decrease of 0.2 percentage points in patients who received placebo (treatment effect 10.6 percentage points; P<0.001). The Subcommittee noted that this treatment effect was maintained throughout the study, with a change in the percent of predicted FEV_1 from baseline at week 48 that was 10.5 percentage points greater in patients who received ivacaftor compared with patients who received placebo (P<0.001). The Subcommittee noted that at week 48, patients who received ivacaftor were less likely to have a pulmonary exacerbation, had a greater improvement in Cystic Fibrosis Questionnaire-revised (CFQ-R) respiratory domain scores, and greater weight gain than patients who received placebo. The Subcommittee noted that the incidence of adverse events was similar between the treatment groups, and that serious adverse events were reported for 24% (n = 20) of patients who received ivacaftor compared with 42% (n = 33) of patients who received placebo.

14.21. The Subcommittee noted the findings of the randomised, double-blind, placebo-controlled, phase 3 ENVISION trial, which evaluated ivacaftor in 52 patients aged 6–11 years with cystic fibrosis and a G551D-CFTR mutation on at least one allele (Davies et al. Am J Respir Crit Care Med 2013;187,11:1219-25). The Subcommittee noted that after 24 weeks of treatment, there was an increase from baseline of 12.6 percentage points in the percent predicted FEV_1 in patients who received ivacaftor compared with an increase of 0.1 percentage points in patients who received placebo (treatment effect 12.5 percentage points; P<0.001). The Subcommittee noted that at 48 weeks, the change from baseline in the percent predicted FEV_1 increased by 10.7 percentage points in patients who received ivacaftor compared with 0.7 in patients who received placebo (treatment effect 10.0

percentage point; P<0.001). The Subcommittee noted that at week 48 patients who received ivacaftor had significantly greater weight gain than patients who received placebo. The Subcommittee noted that the pulmonary exacerbation rate was low and did not differ between treatment groups, and that CFQ-R respiratory domain scores for patients did not differ significantly between treatment groups. The Subcommittee noted that the incidence of adverse events and serious adverse events was similar between treatment groups.

14.22. The Subcommittee noted the findings of PERSIST, a phase 3, open-label extension of the STRIVE and ENVISION trials, which assessed the safety and efficacy of ivacaftor over 96 weeks in 144 adults and adolescents and 48 children with cystic fibrosis and a G551D-CFTR mutation on at least one allele (McKone et al. Lancet Respir Med 2014;2:902-10). The Subcommittee noted that most adverse events were mild or moderate and were consistent with the cystic fibrosis disease state, and that serious adverse events were reported for 20% (n = 38) of patients during the first 48 weeks of PERSIST and 23% (n = 44) of patients during the subsequent 48 weeks. The Subcommittee noted that two adults and one child discontinued treatment due to adverse events, and two deaths occurred during the study. The Subcommittee noted that among adolescents/adults and children who previously received ivacaftor, the change in FEV_1 at week 96 (after 144 weeks of treatment with ivacaftor) was 9.4 and 10.3 percentage points, respectively; and that the absolute increase in weight was 4.1 kg for adolescents/adults and 14.8 kg for children. The Subcommittee noted that the improvement in CFQ-R respiratory domain scores and pulmonary exacerbation rate observed in STRIVE were maintained.

14.23. The Subcommittee noted that the primary and secondary endpoints used in the STRIVE, ENVISION, and PERSIST studies are surrogate measures of outcome, and that there is no indication as to whether the benefits observed will translate to an improvement in survival.

14.24. The Subcommittee noted the findings of an ongoing observational, post-approval safety study which is evaluating the clinical outcomes and disease progression of 1667 ivacaftor-treated and 8269 comparator patients with cystic fibrosis in the US and UK (Bessonova et al., Thorax 2018;73:731-40). The Subcommittee noted the results from the 2014 analyses, 2 and 3 years following the commercial availability of ivacaftor in the UK and USA, respectively. The Subcommittee noted that ivacaftor-treated patients from the US were observed to have lower risks of death (0.6% vs 1.6%, $P = 0.0110$), organ transplantation (0.2% vs 1.1%, $P = 0.0017$), hospitalisation (27.5% vs 43.1%, $P < 0.0001$) and pulmonary exacerbation (27.8% vs 43.3%, $P < 0.0001$) compared with comparator patients; trends were similar in the UK with the exception of no difference in organ transplantation. The Subcommittee noted that cystic fibrosis-related diabetes, bone/joint complications, and hepatobiliary complications were less common in ivacaftor-treated patients in the US and UK and depression was less common in ivacaftor-treated patients in the US. The Subcommittee noted several key microorganisms were less prevalent among ivacaftor-treated patients. The Subcommittee noted that no new safety concerns were identified.

14.25. The Subcommittee considered that there were several limitations associated with the study published by Bessonova et al. (2018) including the open-label observational study design and that the majority of ivacaftor-treated patients had a class III G551D mutation and the majority of the comparators had a class I/II CFTR genotype, which raises some concern regarding comparability.

14.26. The Subcommittee noted additional evidence provided by a retrospective analysis of data from two phase 3 clinical trials over a 3-year period which investigated ivacaftor for the treatment of cystic fibrosis and comparator patients with cystic fibrosis from a US registry (Sawicki et al. Am J Respir Crit Care Med. 2015;192:836-42). The Subcommittee noted that after an initial improvement in percent predicted FEV_1 in patients who received ivacaftor, there was still continued progressive decline in lung function, as is seen in patients not receiving ivacaftor; however, the rate of decline in lung function compared to matched control patients was significantly slower.

14.27. The Subcommittee noted that the data available regarding the safety and efficacy of ivacaftor available at this time remains limited to three years, with no long-term efficacy and safety data available. The Subcommittee considered the available evidence signals significant benefit in regards to morbidity with reductions in surrogate markers such as hospital admissions and pulmonary exacerbations; however, overall survival data is limited. Members considered the data provides a sufficient signal to accept there may be some survival benefit.

14.28. The Subcommittee noted the findings of the open-label, single-arm KIWI study which investigated the safety, pharmacokinetics, and pharmacodynamics of ivacaftor in children aged 2–5 years with cystic fibrosis and a CFTR gating mutation (Davies JC, et al. Lancet Respir Med. 2016;4:107-15). The Subcommittee noted that ivacaftor 50 mg and 75 mg twice daily appeared to be safe in children over a 24-week period in this study, but that longer-term safety data are still required; however, the Subcommittee noted that this study provided adequate evidence for the FDA to approve ivacaftor for children aged 2 to 5 years in March 2015. Members considered that clinicians would be likely to treat children under six years of age with ivacaftor if it was available; however, this would currently be an unapproved indication in New Zealand.

14.29. The Subcommittee noted the high proposed cost of ivacaftor and took this into account in its priority recommendation. The Subcommittee considered that there is a significant unmet need for a disease-modifying treatment for patients with cystic fibrosis and G551D mutation; that the evidence of a health benefit from treatment with ivacaftor is of moderate quality and strength, limited only by a lack of long-term survival data; and that treatment with ivacaftor has the potential to reduce costs associated with pulmonary exacerbations, hospitalisations, and possibly transplant.

14.30. The Subcommittee noted that PHARMAC should seek advice regarding the Special Authority criteria for ivacaftor from physicians who specialise in treating individuals with cystic fibrosis.

14.31. The Subcommittee noted that ivacaftor is being investigated in combination with lumacaftor and tezacaftor for the treatment of a broader range of mutations than the Class III gating mutations, but that these treatment combinations were considered to be outside the scope of the current application.