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

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

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

The Rare Disorders Subcommittee may:

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

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

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

This Subcommittee meeting record will be reviewed by PTAC at its February 2020 meeting.

Present from the Subcommittee

Prof Tim Stokes (Chair, PTAC member)
Dr Melissa Copland (PTAC member)
Prof Carlo Marra
Dr Humphrey Pullon
Dr Howard Wilson
Dr James Cleland
Dr Janice Fletcher
Dr Katherine Neas
Dr William Wong

Apologies

Dr Dylan Mordaunt

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1 The role of PTAC Subcommittees and records of meetings

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

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

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

1.4 The Rare Disorders Subcommittee is a subcommittee of PTAC. The Subcommittee and PTAC and other PTAC Subcommittees have complementary roles, expertise, experience, and perspectives:

- Both PTAC Subcommittees and PTAC are statutory advisory committees established by the PHARMAC Board (external to and separate from PHARMAC staff). Both provide objective advice to PHARMAC on community and hospital pharmaceuticals and their benefits, using the PHARMAC Factors for Consideration. PTAC Subcommittees complement and are separate from PTAC; they are not subordinate.

- PTAC Subcommittees provide objective advice within specific therapeutic areas. PTAC Subcommittees are appointed to reflect specialist knowledge and expertise in health needs and treatments within their own therapeutic groups/areas of clinical practice, including the applicability of evidence to clinical funding settings in New Zealand. The Rare Disorders Subcommittee provides advice in the therapeutic area of rare disorders.

- PTAC Subcommittees make recommendations, including providing a priority, within their therapeutic groups of interest. The Rare Disorders Subcommittee recommends with priority within the rare disorders therapeutic area, as within that area of health need and clinical practice.

- PTAC considers Applications or PHARMAC staff proposals across all therapeutic groups in the Pharmaceutical Schedule. It has an overview view of Applications and other items referred to it for clinical advice. PTAC provides and promotes critical appraisal of strength and quality of evidence, applied rigorously, systematically and consistently across all therapeutic groups.

- PTAC Subcommittees and PTAC therefore provide separate and different, if complementary, perspectives and advice to PHARMAC. PTAC examines the same evidence with a different perspective from specialist expert PTAC Subcommittees, as do Subcommittees between them.

The Rare Disorders Subcommittee and other PTAC Subcommittees may therefore, at times, make recommendations for treatments for rare disorders that differ from PTAC's, including the priority assigned to recommendations, when considering the same evidence. Likewise, PTAC may, at times, make recommendations for treatments for rare disorders

that differ from PTAC Subcommittees', or PTAC Subcommittees may make recommendations that differ from other PTAC Subcommittees'.

PHARMAC considers the recommendations provided by both the Rare Disorders Subcommittee and PTAC and any other relevant PTAC Subcommittees when assessing applications for treatments for rare disorders.

1.5 PHARMAC has established three principles that guide funding applications for medicines for rare disorders:

1. The medicine has been approved by Medsafe, or an approved international regulatory authority, for the identified indication or condition.
2. The disorder is a clinically defined disorder affecting an identifiable and measurable patient population of less than 1:50,000 in New Zealand.
3. The medicine is only registered for the treatment of the rare disorder, or if it is registered for other disorders (or is part of phase three clinical trials for other disorders) it still meets principle 2.

In order for a funding application to be considered by the Rare Disorders Subcommittee as a medicine for a rare disorder, an application would be expected to meet all three principles.

PHARMAC may also choose to seek clinical advice from the Rare Disorders Subcommittee for applications that do not meet the above principles.

2 Summary of recommendations

7.3 The Subcommittee recommended that the application for mercaptamine (cysteamine) hydrochloride 0.55% viscous eye drops (Cystadrops) be declined, based on low quality evidence of benefit and the high proposed cost of Cystadrops compared with the current standard of care (extemporaneously compounded aqueous cysteamine hydrochloride 0.55% eye drops).

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

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

9.3 The Subcommittee recommended that the application for Coenzyme Q10 (CoQ10) for the treatment of CoQ10 deficiency mitochondrial disorders be deferred on the basis of the information supplied.

10.4 The Subcommittee recommended that levocarnitine for carnitine deficiency secondary to therapeutic ketogenic diet for intractable epilepsy be deferred, due to insufficient supporting evidence and uncertainty regarding the size and definition of the intended patient population.

10.5 The Subcommittee recommended that levocarnitine for inborn errors of metabolism be funded with a high priority within the context of the rare disorders therapeutic area, subject to Special Authority criteria.

11.3 The Subcommittee recommended that migalastat be funded with a medium priority in the context of the rare disorders therapeutic area and funding enzyme replacement therapy for Fabry disease, subject to Special Authority criteria.

3 New Subcommittee Member

3.1 The Chair welcomed Dr Katherine Neas, a Clinical Geneticist, as a new member of the Rare Disorders Subcommittee.

4 Record of the Rare Disorders Subcommittee Meeting held on 5 and 6 November 2018

4.1 The Subcommittee noted the previous record of the meeting that took place on 5 and 6 November 2018; and Subcommittee considered it to be an accurate representation of the meeting and were accepted as a true record.

5 Therapeutic Group Review

Previous recommendations of the Rare Disorders Subcommittee

5.1 The Subcommittee noted that the applications it either recommended for decline or gave a positive recommendation for funding at its November 2018 meeting have since been ranked by PHARMAC.

5.2 The Subcommittee noted that PTAC Subcommittees and PTAC may differ in the advice they provide to PHARMAC, including priority of recommendations, due to the committees' different, albeit complementary, roles, expertise, experience, and perspectives (see Section 1).

5.3 Members noted that PTAC had not agreed with the Subcommittee's medium priority recommendation for agalsidase alfa for Fabry disease; and that at its February 2019 meeting, PTAC had considered the application and recommended decline, due to what PTAC considered to be low quality evidence consistent with only modest clinically meaningful long-term health benefits.

5.4 The Subcommittee noted that a resubmission from the supplier of migalastat for Fabry disease was to be considered at this 2019 meeting – see item 10. Members were of

the view that further consideration of any treatments for Fabry disease would need to take into account both enzyme replacement therapy and chaperone agents.

5.5 The Subcommittee noted that PTAC had not agreed with the Subcommittee's medium priority recommendation for ivacaftor for cystic fibrosis with G551D mutation and that at its February 2019 meeting, PTAC had considered the application and recommended funding with low priority. PTAC's recommendation was based on what it considered was high health need, lack of disease-modifying treatment options, moderate quality evidence of health benefit noting the limited availability of long-term data, and concerns regarding markers of surrogacy and high cost. The Subcommittee noted that PHARMAC had asked the supplier of ivacaftor to submit a commercial proposal for cystic fibrosis with G551D mutation, and there had been no response from the supplier to date.

Record of the February 2019 PTAC meeting

5.6 The Subcommittee noted the record of the PTAC meeting held on 21 and 22 February 2019, where the November 2019 Rare Disorder Subcommittee meeting record was considered by PTAC.

Other funding applications of relevance considered by PTAC or its Subcommittees

5.7 The Subcommittee noted the May 2019 meeting record of the Cardiovascular Subcommittee with regard to a clinician application for tafamidis for ATTR (transthyretin) cardiac amyloidosis. The Rare Disorders Subcommittee noted that the Cardiovascular Subcommittee had recommended the funding of tafamadis for the treatment of ATTR cardiac amyloidosis with a medium priority. The Rare Disorders Subcommittee considered there was uncertainty in patient numbers and that it was likely at least 100 people in New Zealand would have this condition, and that rates of diagnosis were likely to increase in future. Subcommittee members considered they had less experience with cardiac amyloidosis in their clinical practices, and as a condition that did not meet PHARMAC's definition of rare disorders it remained more appropriate for tafamidis for ATTR cardiac amyloidosis to be considered by the Cardiovascular Subcommittee. The Rare Disorders Subcommittee observed, however, that the proposed Special Authority criteria proposed by the Cardiovascular Subcommittee included a note regarding medicines that should not be used in combination with tafamidis. The Rare Disorders Subcommittee considered that including a note of this nature would be inconsistent with funding criteria for other medicines in the Pharmaceutical Schedule, which do not caution for drug interactions etc. because as a funding tool (not a pharmacopoeia) such criteria are non-exhaustive for safety. The Rare Disorders Subcommittee recommended that PHARMAC staff engage with the supplier of tafamidis to ascertain the regulatory approval plans for this medicine.

Other funded treatments for rare disorders

5.8 The Subcommittee noted that twelve pharmaceuticals are currently listed on the Pharmaceutical Schedule for use in various rare disorders, and that a number of other treatments are funded via the Named Patient Pharmaceutical Assessment (NPPA) exceptional circumstances pathway.

NPPA review

5.9 The Subcommittee noted an overview from PHARMAC staff about NPPA applications for individual patients with rare disorders. NPPA provides an alternative pathway to funding medicines for individual patients who have exceptional clinical circumstances. Members considered that this was useful for identifying potential medicines that could be considered for listing in the Pharmaceutical Schedule.

5.10 The Subcommittee noted that there have been several NPPA applications for levocarnitine for various metabolic disorders and that a clinician funding application for Schedule listing was being considered at this meeting.

5.11 Members noted that NPPA remains an option to access treatments for rare disorders for individual patients, providing that applications meet the prerequisites of the NPPA policy.

Other rare disorder medicines being considered for Schedule listing

Trientine for Wilson's disease

5.12 The Subcommittee noted that trientine is currently funded for individuals with Wilson's disease through NPPA for community-based patients who are intolerant to penicillamine and zinc. Trientine is listed in Section H of the Pharmaceutical Schedule (Hospital Medicines List) primarily for initiation of treatment, but no supply contract is in place and there is currently no Medsafe approved product.

5.13 The Subcommittee noted that PHARMAC staff had proposed the following funding criteria for trientine, based on expert clinical advice:

> Special Authority for Subsidy / Hospital restriction
>
> **Initial application** only from a gastroenterologist or hepatologist. Approvals valid for 6 months for applications meeting the following criteria:
> All of the following:
> 1. Patient has confirmed Wilson's disease; and
> 2. Treatment with D-penicillamine has been trialled and discontinued because of unacceptable side effects or an inadequate clinical response measured by urinary copper excretion; and
> 3. Treatment with zinc has been trialled and discontinued because of unacceptable side effects or an inadequate clinical response, or zinc is considered inappropriate as the patient has symptomatic liver disease and requires copper chelation.
>
> **Renewal** only from a gastroenterologist or hepatologist. Approvals valid without further renewal unless notified where the treatment remains appropriate and the patient is benefitting from treatment.

5.14 Members noted that two suppliers of trientine had recently submitted alternative funding criteria to PHARMAC and neither criteria included the requirement to trial or consider treatment with zinc. The Subcommittee considered that it remains appropriate for zinc to be part of treatment regimens at this time. Members were supportive of PHARMAC's proposed funding criteria for trientine and did not recommend any changes.

5.15 The Subcommittee considered that PHARMAC's estimate of 6 to 8 patients with Wilson's disease who would require treatment with trientine over the next five years was reasonable. Members were of the view that patients presenting with clinical symptoms are generally fewer than the prevalence of Wilson's disease stated in the scientific literature.

5.16 The Subcommittee noted that one supplier has recently submitted an evaluation dossier to Medsafe to seek registration of its brand of trientine. Members noted that while cold storage is not required for that supplier's product, it does contain a different salt of trientine and subsequently a different base amount of trientine.

5.17 The Subcommittee advised PHARMAC that when considering the clinical appropriateness of trientine products, PHARMAC should take into account the amount of active ingredient present. Members noted this is a suitability requirement for both clinicians and patients, as it enables consistency in dose adjustments with less likelihood of error occurring in dose calculations.

Carglumic acid for hyperammonaemias and Nitisinone for tyrosinaemia type 1

5.18 Members noted that, at the time of this meeting, there were no Medsafe approved brands of either medicine available in New Zealand, and that two generic suppliers had submitted funding applications for carglumic acid and nitisinone at the November 2018 meeting of the Rare Disorders Subcommittee.

Horizon scanning of therapies for rare disorders

5.19 The Subcommittee noted that avacopan is undergoing investigation in a Phase 3 clinical trial for the rare condition of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis.

5.20 The Subcommittee advised that there is increasing interest in the use of eculizumab for Guillain-Barré syndrome; and that the recent FDA approval of a similar but longer acting agent (ravulizumab-cwvz) may offer an opportunity for competitive pricing of eculizumab. Members noted that PHARMAC had previously considered a funding application for eculizumab for paroxysmal nocturnal haemoglobinuria, which was declined due its high price and resultant low cost effectiveness relative to other new medicines being considered for funding at the time.

5.21 The Subcommittee advised that gene therapy for spinal muscular atrophy is undergoing clinical trials.

Stakeholder engagement and related rare disorders work

5.22 The Subcommittee noted that PHARMAC continues to engage with specialist clinicians, patient advocacy groups and pharmaceutical suppliers in relation to rare disorders. Members also noted the 2019 report recently published by PHARMAC that outlines the international and national rare disorders landscape.

6 Correspondence / Matters arising

Carglumic acid for organic acidaemias

6.1 The Subcommittee noted correspondence from a supplier (Te Arai) in relation to its carglumic acid application for organic acidaemias that was considered by the Subcommittee at the November 2018 meeting. The supplier provided two articles (Chakrapani et al 2018; Blair 2019) that were published since the Subcommittee met, and suggested changes to the proposed funding criteria for carglumic acid when used for organic acidaemias.

6.2 The Subcommittee noted that the supplier's changes to the proposed funding criteria were to enable carglumic acid to be used continuously and that the proposed changes removed the requirement to consider ammonia scavenging therapies first-line.

6.3 The Subcommittee reviewed the published articles and considered these provided insufficient evidence of acceptable strength and quality to change the Subcommittee's previous advice (namely that consideration of ammonia scavenging therapies in patients with organic acidaemias is clinically appropriate). Members further noted that the European guidelines for the treatment of organic acidaemias continue to recommend the first-line use of ammonia scavenging therapies. The Subcommittee, therefore, did not support the supplier's changes to the proposed funding criteria.

6.4 The Subcommittee noted that the supplier used sodium phenylbutyrate as the cost comparator to suggest that carglumic acid would have a similar or lower treatment cost. Members considered that sodium phenylbutyrate was an inappropriate comparator to use in this context as it is well-recognised as being a higher cost treatment for organic acidaemias, and that there is a less expensive commonly-used comparator.

6.5 The Subcommittee reiterated that it had reviewed all the available relevant evidence for carglumic acid for organic acidaemias at its November 2018 meeting and specifically had not recommended carglumic acid for continuous use as the evidence base is weak. Members considered the new information insufficient to change their advice or previous recommendations.

7 Mercaptamine (cysteamine) hydrochloride 0.55% viscous eye drops for the treatment of cystinosis

Application

7.1 The Subcommittee reviewed an application from Recordati Rare Diseases for the funding of mercaptamine (cysteamine) hydrochloride 0.55% viscous eye drops (Cystadrops) for the treatment of cystinosis.

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

Recommendation

7.3 The Subcommittee recommended that the application for mercaptamine (cysteamine) hydrochloride 0.55% viscous eye drops (Cystadrops) be declined, based on low quality evidence of additional benefit and the high proposed cost of Cystadrops compared with the current standard of care (extemporaneously compounded aqueous cysteamine hydrochloride 0.55% eye drops).

Discussion

7.4 The Subcommittee noted that cystinosis is a lysosomal storage disorder in which cystine crystals accumulate in various tissues including the kidneys and eyes.

7.5 The Subcommittee noted that three forms of cystinosis have been described: infantile (nephropathic) cystinosis, late-onset (juvenile) cystinosis, and adult (ocular) cystinosis. The Subcommittee considered that all patients with cystinosis, regardless of subtype, develop cystine crystals in the cornea which requires treatment.

7.6 The Subcommittee noted that, without treatment, cystine crystals begin to accumulate within the cornea in infancy (depending on the type of cystinosis). The Subcommittee noted that the crystals themselves have minimal impact on visual acuity, but that secondary effects can include photophobia, blepharospasm, pain, foreign body sensation, punctate keratopathy, filamentary keratopathy, peripheral corneal neovascularisation, and recurrent corneal erosions.

7.7 The Subcommittee noted that the primary treatment for cystinosis is systemic cysteamine, which preserves renal function and prevents many of the other sequelae associated with cystinosis but does not reduce the accumulation of cystine crystals in the cornea. The Subcommittee noted that topical treatment with eye drops is therefore required in addition to systemic cysteamine to manage the progressive ophthalmologic involvement.

7.8 The Subcommittee noted that there are currently five children and five adults diagnosed with cystinosis in New Zealand, and that the incidence is estimated to be less than one in every 100,000 live births. The Subcommittee considered that there may be one new patient diagnosed with cystinosis every two to three years. The Subcommittee noted that cystinosis is considered to be a pan-ethnic condition.

7.9 The Subcommittee noted that Cystadrops is not currently approved by Medsafe, but that the product has regulatory approval in the European Union for the treatment of corneal cystine crystal deposits in adults and children from 2 years of age with cystinosis. The Subcommittee noted that Cystadrops is not approved for any indication other than cystinosis.

7.10 The Subcommittee considered that the funding application for Cystadrops met PHARMAC's principles for rare disorders.

7.11 The Subcommittee noted that the current standard of care for the treatment of corneal cystine crystals in New Zealand is an unfunded, unlicensed, preservative-free aqueous cysteamine hydrochloride 0.55% eye drop product that is compounded by Optimus Healthcare Limited. The Subcommittee considered that the recommended administration of this product is one drop in each eye at least four to five times daily.

7.12 The Subcommittee noted that cysteamine eye drops reduce corneal cystine crystal accumulation by acting as a cysteine-depleting agent by converting cystine to cysteine-cysteamine mixed disulfides.

7.13 The Subcommittee noted that a number of patients with cystinosis in New Zealand are currently receiving funding for aqueous cysteamine eye drops through the Named Patient Pharmaceutical Assessment (NPPA) mechanism.

7.14 The Subcommittee noted the findings of a Phase 1/2a, open label, crossover, dose response trial that investigated the safety and efficacy of Cystadrops (viscous cysteamine hydrochloride 0.55%) compared with aqueous cysteamine hydrochloride 0.1% eye drops for the treatment of corneal complications in eight patients with infantile nephropathic cystinosis (Labbé et al. Mol Genet Metab. 2014;111:314-320). The Subcommittee noted that patients received aqueous cysteamine hydrochloride 0.1% eye drops four times daily for one month and then switched to Cystadrops at the same dose frequency for 48 months. The Subcommittee noted that after switching to Cystadrops, the in vivo confocal microscopy (IVCM) score decreased by a mean of 28.6% at Day 90 (P<0.0001), a difference which was maintained over 48 months of treatment with Cystadrops. The Subcommittee considered that this likely represented some improvement in visual symptoms but were unsure of the clinical relevance of IVCM as a measure of efficacy. The Subcommittee noted that no serious adverse events were observed during the study.

7.15 The Subcommittee noted the findings of an open-label, randomised, two-armed, Phase 3 trial that investigated the efficacy of Cystadrops (viscous cysteamine hydrochloride 0.55%) compared with aqueous cysteamine hydrochloride 0.1% eye drops administered four times daily for 90 days in 31 patients with cystinosis (Liang et al. Invest Opthalmol Vis Sci. 2017;58:2275-83). The Subcommittee noted that the mean absolute change in IVCM at Day 90 was -4.6 (±3.1) in the group receiving Cystadrops compared with -0.46 (±3.38) in the group receiving aqueous eye drops (P<0.0001). The Subcommittee noted that photophobia, corneal cysteine crystal scores, and corneal cystine crystal depth were significantly improved in the group receiving Cystadrops compared with the group receiving aqueous cysteamine eye drops. The Subcommittee noted that four serious adverse events were reported, but none were considered related to treatment. The Subcommittee considered that 90 days was a short follow-up period for a chronic condition that likely requires life-long treatment.

7.16 The Subcommittee considered that the two studies described above provide the primary evidence for the benefits associated with Cystadrops. However, the Subcommittee considered that the use of products with different concentrations of cysteamine hydrochloride (0.55% viscous vs 0.1% aqueous) limits the value of these studies, as any improvement in outcome is likely to be due to a higher concentration of the active ingredient as opposed to the formulation of the product. The Subcommittee noted the supplier's explanation that the 0.1% aqueous product was the standard of care at the time in the country where the studies were performed, but also noted that the 0.1% aqueous product has since been removed from the market due to its failure to show efficacy in treating corneal cystine crystals.

7.17 The Subcommittee considered that there would be benefits associated with having an eye drop product that required fewer instillations per day (ideally once daily), particularly for young children where administration is difficult; however, it was not clear to the Subcommittee whether the use of Cystadrops would enable a meaningful reduction in the number of daily installations required given that real-world practice indicates that the aqueous product is often only administered four times daily.

7.18 The Subcommittee noted that Cystadrops does not require refrigeration, which may have benefits compared with the aqueous formulation, but also noted that the shelf-life (once opened) of Cystadrops is only 7 days compared with 28 days for the aqueous formulation if properly stored.

7.19 The Subcommittee considered that the proposed price for Cystadrops was approximately 18-fold higher than the cost of the aqueous eye drop product currently used in New Zealand, which is a significant incremental difference for uncertain benefits.

7.20 The Subcommittee considered that the currently available evidence for Cystadrops is of low quality due to the comparator in the pivotal trials having a significantly lower concentration of cysteamine hydrochloride than both Cystadrops and the currently funded alternative. The Subcommittee considered there was a theoretical suitability benefit associated with the use of a viscous formulation, but that this benefit did not outweigh the significant cost of Cystadrops.

7.21 The Subcommittee noted that any further consideration of the proposal would need to include both additional evidence demonstrating that Cystadrops requires fewer daily instillations with equivalent or superior efficacy to the currently available aqueous formulation, and a revised price with cost-effectiveness comparable to that of the aqueous formulation.

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

Application

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

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

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

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

Re-assessment required after 12 months

All of the following:

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

Continuation – spinal muscular atrophy (SMA) – pre-symptomatic
Applications only from, or in consultation with, a specialist medical practitioner experienced in the diagnosis and management of SMA associated with a neuromuscular clinic of a recognised hospital in the management of SMA.
Re-assessment required after 12 months
All of the following:
1. Patient must have had a previous approval for nusinersen; and
2. Treatment must be given concomitantly with standard of care for this condition; and
3. There has been demonstrated maintenance of motor milestone function (as assessed using age-appropriate scales: the HINE Section 2, CHOP INTEND, or HFMSE) since treatment initiation; and
4. The patient does not require invasive permanent assisted ventilation (see Note).

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

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

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

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

Re-assessment required after 12 months
All of the following:
1. Genetic documentation of 5q SMA homozygous gene deletion, homozygous mutation, or compound heterozygous mutation; and
2. Patient must have experienced the defined signs and symptoms of SMA type I, II or IIIa prior to 3 years of age (see Notes); and
3. Treatment must be given concomitantly with standard of care for this condition; and
4. Treatment must not exceed four loading doses (at days 0, 14, 28 and 63); and
5. Patient must be 18 years of age or under.

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

All of the following:

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

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

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

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

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

Discussion

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

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

8.7 The Subcommittee noted that the resubmission requested that the proposed eligibility criteria for nusinersen be widened from the original submission, which was for paediatric patients (18 years or under) with spinal muscular atrophy (SMA) types I, II, or IIIa with symptom onset before three years of age, to include pre-symptomatic individuals who have been genetically diagnosed with SMA.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

8.14.1 The Subcommittee noted that they had previously considered results from the CHERISH-SHINE study after a median treatment duration of 441.5 days (30 June 2017 data cut). At the current meeting, the Subcommittee considered data from CHERISH-SHINE after a median duration of 1175 days (15 October 2018 data cut); these results were presented at the 2019 American Academy of Neurology Annual Meeting (Darras et al. Interim Report on the Safety and Efficacy of Longer term Treatment With Nusinersen in Later onset Spinal Muscular Atrophy (SMA): Results From the SHINE Study. Presented at: 71st American Academy of Neurology (AAN) Meeting. May 4 10, 2019 | Philadelphia, PA. P063).

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

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

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

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

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

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

8.17 The Subcommittee considered that the clinical trials investigating nusinersen are of good strength and quality. The Subcommittee noted that despite the follow-up being limited to a duration of less than four years, the updated data indicates that the

treatment response is likely to be durable. The Subcommittee also considered that the magnitude of benefit observed in the clinical trials compared with the natural history of the disease gives confidence that nusinersen is likely to provide a clinically meaningful benefit.

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

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

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

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

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

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

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

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

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

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

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

8.29 The Subcommittee considered that, due to the magnitude of benefit reported in the updated analyses from the NURTURE, ENDEAR-SHINE and CHERISH-SHINE trials, that the data was robust enough to inform a recommendation for pre-symptomatic and symptomatic patients. The Subcommittee considered that there is good quality evidence that treatment with nusinersen improves survival, reduces the risk of ventilation, and maintains motor function in patients with pre-symptomatic and infantile-onset SMA and improves motor function in patients with childhood-onset SMA. The Subcommittee also considered that the greatest benefit is likely to be observed in the pre-symptomatic stage.

9 Coenzyme Q10 – application for mitochondrial diseases

Application

9.1 The Subcommittee reviewed a clinician application for Coenzyme Q10 (CoQ10) for the treatment of CoQ10 deficiency mitochondrial disorders.

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

Recommendation

9.3 The Subcommittee recommended that the application for Coenzyme Q10 (CoQ10) for the treatment of CoQ10 deficiency mitochondrial disorders be deferred on the basis of the information supplied.

9.3.1 The Subcommittee made this recommendation because, in order to fully consider this application, it would need a clearer definition of the intended patient population that would benefit from CoQ10 treatment, along with evidence supporting the use of CoQ10 in that patient population, if available. The Subcommittee noted that, while there is very little evidence available, it would welcome a resubmission from the applicant that addresses the gaps identified by members.

Discussion

9.4 The Subcommittee noted that mitochondrial disorders are rare, chronic, relapsing diseases caused by mutated or insufficient mitochondrial DNA that affect the mitochondrial respiratory chain process; these disorders result in inadequate production of adenosine triphosphate (ATP) for essential cellular processes including those in muscle and nerve tissues. Members considered that there are many mitochondrial disorders with substantial variations between types, and that in general these are poorly understood.

9.5 The Subcommittee noted that coenzyme Q10 (CoQ10) is a fat-soluble compound produced in the body and obtained from dietary intake, which acts as an antioxidant in cell membranes and is a key component of mitochondrial respiration, producing energy as ATP. The Subcommittee noted that CoQ10 is also known as ubiquinone or ubidecarenone.

9.6 The Subcommittee noted that primary CoQ10 deficiency mitochondrial disorders (also called CoQ10 synthesis disorders) result from mutations in genes that are involved in CoQ10 synthesis, called the COQ genes, and that secondary CoQ10 deficiency mitochondrial disorders result from mutations in genes that are not directly related to CoQ10 synthesis. The Subcommittee noted the applicant has provided two publications regarding CoQ10 deficiency disorders:

- Desbats et al. J Inherit Metab Dis. 2015;38:145-56
- Salviati et al. GeneReviews [Internet]. 2017 [cited Sept 2019]

9.7 The Subcommittee noted that mitochondrial disorders, including CoQ10 deficiency disorders, can quickly lead to serious complications and organ damage (eg diabetes, cardiovascular disease, myopathy, renal and liver disease). The Subcommittee noted that the impact on an individual and their family/whānau depends on the genetic basis of the disease, age at onset and extent of organ involvement. The Subcommittee noted that young children with CoQ10 synthesis disorders are more likely to present with severe disease, multi-organ involvement and will have high morbidity and mortality if not treated.

9.8 The Subcommittee noted that there are no disease-modifying treatments for CoQ10 deficiency disorders, and that standard care includes management of complications and

use of supplements to reduce damage to mitochondria, improve energy regeneration or remove toxin build-up.

9.9 The Subcommittee noted that CoQ10 is not approved by Medsafe, that it is considered a dietary supplement in New Zealand, that it can be purchased over the counter at pharmacies in a variety of doses and formulations.

9.10 The Subcommittee noted that CoQ10 is not listed in the Pharmaceutical Schedule for any indication, and noted that there is no evidence of consideration by international pharmaceutical funding agencies regarding CoQ10 for mitochondrial disorders, except for one assessment by the National Institute of Health and Care Excellence (NICE), UK (Mitochondrial disorders in children: Co-enzyme Q10 [Internet]. Evidence Summary e11. UK: NICE; March 2017 [cited Sept 2019]).

9.11 The Subcommittee noted that PHARMAC has received Named Patient Pharmaceutical Assessment (NPPA) applications for CoQ10 use in a variety of dose forms (eg tablet, capsule, oral liquid) in patients with a range of mitochondrial disorders. The Subcommittee noted that while most applications were for children, patient age at the time of application ranged from 10 months to 41 years, that the average requested dosage was 360 mg per day (median 300 mg per day), and that most applications had been approved.

9.12 The Subcommittee noted that the applicant had requested CoQ10 capsules (stating that availability of additional dose forms as well would be preferred) for the treatment of approximately 10 patients per year with suspected or known mitochondrial disorders with possible or known CoQ10 responsiveness, and had proposed dosing that ranges from 10 mg per kg up to 100 mg per kg per day. The Subcommittee noted that the applicant had stated that patients with a mitochondrial disorder can present with “any symptom, in any organ at any age” making it difficult for metabolic paediatricians to exclude a CoQ10 deficiency disorder, and as such, had proposed that such patients would commence treatment with CoQ10 while awaiting confirmation of a diagnosis.

9.13 The Subcommittee considered that primary CoQ10 deficiency disorders are the likely intent of this application, however, the proposed patient population in New Zealand had not been further defined by the applicant. The Subcommittee considered that, if restricted to include only patients with the primary CoQ10 deficiency disorders, and assuming 10 patients per year plus one new diagnosis per year (which was considered a reasonable estimate), then the prevalence of primary CoQ10 deficiency disorders would be less than 1 in 50,000 in New Zealand; and this indication would meet the definition of a rare disorder as per the second of PHARMAC’s Three Principles for Rare Disorders.

Evidence

9.14 The Subcommittee noted the results of a 2012 Cochrane review (Pfeffer et al. Cochrane Database Syst Rev. 2012. 18: CD004426), which included 12 studies and aimed to determine whether there is objective evidence to support the use of current treatments, including CoQ10, for mitochondrial disorders. The Subcommittee noted that the authors concluded there was no clear evidence that supported the use of any intervention in mitochondrial disorders and that further research is needed.

9.15 The Subcommittee noted that in 2017, NICE reviewed the evidence for CoQ10 for the treatment of children with mitochondrial disorders and considered this included the best

available evidence for adults and young people, comprising of three randomised controlled trials and three case reports in a total of six children (Mitochondrial disorders in children: Co-enzyme Q10 [Internet]. Evidence Summary e11. UK: NICE; March 2017 [cited Sept 2019]). Members considered that the case reports suggested a benefit, but the clinical significance of these results was unclear.

9.16 The Subcommittee reviewed the following three trials that were included in the NICE 2017 evidence summary:

9.16.1 The Subcommittee noted the results of a randomised, controlled, 60-day crossover study in 30 adults with mitochondrial disorders who received CoQ10 600 mg twice daily or placebo (Glover et al. 2010). The Subcommittee considered this trial provided meaningful evidence, however, there was no statistically significant benefit for CoQ10 compared with placebo for mitochondrial disease-specific activities of daily living (P=0.26) and quality of life (P=0.09) assessment scores, mean maximal isometric forearm strength (P=0.27) or other surrogate endpoints.

9.16.2 The Subcommittee noted the results of a controlled, 60-day crossover study in 8 patients (adults and young people) with mitochondrial encephalomyopathies who received CoQ10 160 mg daily for 3 months and placebo for 1 month (Chen et al. 1997). The Subcommittee noted that the authors concluded that there were no statistically significant differences (*P* values not published) between CoQ10 and placebo in regard to fatigue in activities of daily living score or sustained endurance strength. The Subcommittee noted that the 2012 Cochrane review (paragraph 1.15, above) had excluded this trial due to what the authors considered to be high risk of bias due to non-randomisation, poor study design and potential selective outcome reporting.

9.16.3 The Subcommittee noted the results of an open-label, single-arm study in 44 patients (adults and young people) with mitochondrial myopathies who received CoQ10 2 mg per kg daily for 6 months, designed to select those patients who responded to therapy (Bresolin et al. 1990). The Subcommittee noted there was a statistically significant increase in the global Medical Research Council scale for muscle strength after 6 months treatment with CoQ10 ($P<0.01$) and a small but significant reduction in serum lactate between baseline and 9 months ($P<0.01$), however, the 2017 NICE evidence summary considered that the clinical significance of these changes was unclear. The Subcommittee noted that the 2012 Cochrane review had excluded this trial, due to what the authors considered to be lack of randomisation and high risk of bias due to poor methodology.

9.17 The Subcommittee noted that the individual trials included in the 2017 NICE evidence summary (Glover et al. 2010, Chen et al. 1997 and Bresolin et al. 1990) did not provide safety or tolerability data, however, the 2017 NICE evidence summary indicated that CoQ10 may reduce insulin requirements in people with diabetes, may enhance or reduce the anticoagulant effect of warfarin, and that possible side effects of CoQ10 include nausea, diarrhoea, gastric reflux.

9.18 The Subcommittee noted that NICE had stated in its evidence summary that the evidence available was insufficient to confirm the place of CoQ10 in the treatment of children with mitochondrial disorders. The Subcommittee considered that there were no other

randomised controlled trials or higher-quality data available for the use of CoQ10 in children.

9.19 Members considered that the three clinical trials in the NICE 2017 evidence summary used surrogate endpoints (eg muscle strength and lactate levels), and that no evidence was available for long-term efficacy or safety of CoQ10 in these patient groups and no evidence of any significant effects on morbidity or mortality.

9.20 The Subcommittee considered that the evidence for CoQ10 for the treatment of CoQ10 deficiency disorders (including primary CoQ10 synthesis disorders) was heterogenous and of low quality, and that the evidence did not support use in the broad patient population requested by the applicant because the health benefit was unclear. However, members considered that performing high-quality, randomised, controlled trials in this heterogenous patient population is challenging. Members noted that more than 150 genes are involved in the respiratory chain process making trial recruitment difficult and considered that evidence from small, lower-quality studies should be evaluated.

9.21 Members considered that patients with primary CoQ10 deficiency disorders may respond best to CoQ10. Members considered that CoQ10 may offer less benefit for patients with secondary CoQ10 deficiency disorders, but that clinicians would likely wish to trial CoQ10 in patients with secondary CoQ10 deficiency disorders or other mitochondrial disorders, although these patients may receive little or no benefit from it.

General

9.22 The Subcommittee considered that the applicant's requested dosing of 10 mg to 100 mg per kg per day was high compared with published doses, which are predominantly 5 mg to 50 mg per kg per day. The Subcommittee considered that the optimal dosing remained unclear and that this would impact the cost-effectiveness of CoQ10.

9.23 The Subcommittee noted that use of soluble forms, soft gel caps or oily formulations of CoQ10 (and not tablets) are proposed as the best formulations to use in patients with CoQ10 deficiency mitochondrial disorders due to higher CoQ10 bioavailability (Desbats et al. J Inherit Metab Dis. 2015;38:145-56).

9.24 The Subcommittee considered that, if funded, listing CoQ10 on the Pharmaceutical Schedule would provide funded access to a pharmaceutical-grade product, and that it could remove the need to submit NPPA applications for CoQ10 for these patients, saving clinician time and effort and providing greater certainty and timeliness for patients.

9.25 Members also considered that if CoQ10 treatment was effective over the long term, then it could confer significant health sector cost savings, and savings and benefits to patients and to family/whānau (eg from reduced hospital visits or care costs). However, Members noted that assessing and quantifying the effectiveness of CoQ10 treatment would be difficult.

9.26 The Subcommittee considered that there would be a minimal pharmaceutical budget impact from treating suspected cases of CoQ10 deficiency disorders whose mutation test results would be negative and who would subsequently discontinue CoQ10 treatment.

9.27 The Subcommittee considered that, if funded, CoQ10 would not replace any other treatments but would be additive to any currently used for patients with mitochondrial disorders (eg riboflavin, L-taurine, L-arginine, thiamine, vitamins C and E which are not funded and would be considered through the NPPA pathway) and any other treatments used for the management of disease manifestations.

9.28 The Subcommittee considered that the over-the-counter use of CoQ10 is broad and that, if funded, robust Special Authority criteria would be required to ensure CoQ10 access for the patient population that would benefit the most. The Subcommittee considered that paediatric neurologists would also be appropriate prescribers. The Subcommittee noted that PHARMAC had provided draft Special Authority, and members considered that it would need to be revised if new information or evidence is received.

9.29 The Subcommittee considered that the information provided in the application did not define the target patient population sufficiently or identify the patients who would benefit the most from this treatment, and at what dose. The Subcommittee conveyed that it was open to reviewing a resubmission, if received, that ideally included an updated definition of the intended patient population with primary CoQ10 deficiency disorders, and considered that this would help manage the risk associated with the low level of evidence.

9.30 The Subcommittee considered that patients who currently receive funded CoQ10 for a mitochondrial disorder via the NPPA process should continue treatment with CoQ10 if they are receiving a benefit. Members considered that the number of treatments used concurrently to manage these patients' disease would make it difficult to assess the true benefit of CoQ10 addition, due to confounding.

10 Levocarnitine for use in ketogenic diet support and metabolic indications

Application

10.1 The Subcommittee reviewed a clinician application for levocarnitine for carnitine deficiency secondary to therapeutic ketogenic diet for intractable epilepsy.

10.2 The Subcommittee also considered levocarnitine for use in metabolic indications, specifically, for patients with inborn errors of metabolism (a PHARMAC-initiated application).

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

Recommendation

10.4 The Subcommittee recommended that levocarnitine for carnitine deficiency secondary to therapeutic ketogenic diet for intractable epilepsy be deferred, due to insufficient supporting evidence and uncertainty regarding the size and definition of the intended patient population.

10.4.1 The Subcommittee made this recommendation because, in order to fully consider this application, it would need a clearer definition of the appropriate target patient population (eg carnitine deficiency due to valproate and plasma carnitine less than 26 micromoles per litre) and evidence of effectiveness or use of levocarnitine in

that defined patient population. The Subcommittee noted it would welcome a resubmission from the applicant that addresses these matters.

10.5 The Subcommittee recommended that levocarnitine for inborn errors of metabolism be funded with a high priority within the context of the rare disorders therapeutic area, subject to the following Special Authority criteria:

> **Initial application** – inborn errors of metabolism. Only from a metabolic physician or medical physician on the recommendation of a metabolic physician.
> Approvals valid for 6 months for applications meeting the following criteria:
> 1. Patient has a confirmed primary carnitine deficiency; and
> 2. Plasma carnitine levels are less than the lower limit of normal.
>
> **Renewal application** – inborn errors of metabolism. Only from a metabolic physician or on the recommendation of a metabolic physician. Approvals valid without further renewal unless notified where the treatment remains appropriate and the patient is benefiting from treatment.

10.5.1 The Subcommittee made this recommendation because of the high health need of patients, especially those with carnitine transport or uptake deficiencies (eg systemic primary carnitine deficiency (CDSP)) for whom levocarnitine is the only beneficial treatment and there is evidence of harm if patients are untreated. The Subcommittee noted that a pharmaceutical-grade (GMP-certified) product or products would need to be identified in order for levocarnitine to be considered for listing in Section B of the Pharmaceutical Schedule.

Discussion

10.6 The Subcommittee noted that levocarnitine, the only biologically active isomer of carnitine, is not approved by Medsafe. It is considered a dietary supplement in New Zealand and can be purchased over the counter at pharmacies or online.

10.7 The Subcommittee noted that carnitine is a compound that is synthesised in the body from amino acids and is also obtained from the diet, particularly from meat and animal products. The Subcommittee noted that carnitine transports long-chain fatty acids into the mitochondria of tissue cells, especially to skeletal and cardiac muscle cells, enabling oxidation of the fatty acids and energy metabolism.

10.8 The Subcommittee noted that levocarnitine is not listed in Section B of the Pharmaceutical Schedule for community use in any indication and noted that there is no evidence of consideration by international pharmaceutical funding agencies regarding levocarnitine. The Subcommittee noted that levocarnitine is funded for hospital use in multiple dose forms (capsules, oral solution and solution for injection) and that these dose forms ensure there is a suitable formulation for use in children.

10.9 The Subcommittee noted that testing of total plasma carnitine is performed in New Zealand with an approximate cost of up to $150 per test. Members noted that the normal reference range for plasma total carnitine is between 35 and 60 micromoles per litre (umol/L). Members considered that plasma carnitine may not accurately reflect total body carnitine due to stores in muscle tissue.

Carnitine deficiency secondary to ketogenic diet

10.10 The Subcommittee noted that a ketogenic diet is a high-fat, low-carbohydrate dietary regimen designed to mimic the metabolic changes that occur during fasting, and that this diet may be used as conjunctive therapy for patients with severe epilepsy who have not achieved seizure control with treatment (ie intractable epilepsy). The Subcommittee noted that about two-thirds of patients with intractable epilepsy experience a positive response to a ketogenic diet.

10.11 The Subcommittee considered that a therapeutic ketogenic diet may result in carnitine deficiency due to its high fat content, however, members considered that symptomatic carnitine deficiency rarely occurs due to a ketogenic diet.

10.12 The Subcommittee noted that carnitine deficiency has also been reported in patients with epilepsy who have received valproate, carbamazepine and phenobarbital. The Subcommittee considered that the majority of New Zealand patients with intractable epilepsy would be carnitine deficient due to use of valproate, which creates a fatty acid oxidation defect.

10.13 The Subcommittee noted that PHARMAC has received Named Patient Pharmaceutical Assessment (NPPA) applications for levocarnitine use in patients aged 5 to 12 years with carnitine deficiency secondary to a therapeutic ketogenic diet for intractable epilepsy, with requested dosages ranging from 10 mg to 50 mg per kg per day.

10.14 The Subcommittee noted that in December 2017 the Special Foods Subcommittee stated that there are two DHBs (Auckland and Canterbury) that have dedicated teams for managing patients on therapeutic ketogenic diets; and that they commence approximately 12-16 patients (at Starship Children's Hospital) and 10-30 patients (at Christchurch Hospital) on these diets annually. Members considered that the true potential patient population in New Zealand would be higher as patients in other cities or regions are currently unable to access ketogenic diet therapy for intractable epilepsy.

10.15 The Subcommittee noted the applicant has estimated that there would be 20 to 30 patients per year in Christchurch. The Subcommittee noted and expressed some uncertainty about PHARMAC's estimate of 53 patients nationally per year who might commence and respond to a therapeutic ketogenic diet (estimate weighted for response and accounts for 2 years of treatment).

10.16 The Subcommittee considered that this indication (carnitine deficiency secondary to a therapeutic ketogenic diet for intractable epilepsy) does not meet the definition of a rare disorder as per the second of PHARMAC's Three Principles for Rare Disorders.

10.17 The Subcommittee noted the following publications regarding management of patients with intractable epilepsy who are on a ketogenic diet, and for the treatment of carnitine deficiency secondary to therapeutic ketogenic diet for intractable epilepsy:

- Vining EP. Epilepsy Res. 1999;37:181-90
- Kossoff et al. Epilepsia. 2009;50:304-17
- Kosoff et al. Epilepsia Open. 2018;3:175-92
- Martin-McGill et al. Cochrane Database Syst Rev. 2018;11:CD001903

- Epilepsy Guidelines and Pathways for Children and Young People [Internet]. New Zealand: Child and Youth Clinical Networks (NZCYCN); 2017 [cited September 2019]
- Epilepsies: diagnosis and management [Internet]. Clinical guideline CG137. UK: National Institute for Health and Care Excellence (NICE); Jan 2012 [revised Oct 2019; cited Sept 2019]

10.18 The Subcommittee considered that there is no high-quality evidence for levocarnitine supplementation for patients with carnitine deficiency secondary to therapeutic ketogenic diet for intractable epilepsy, but that there are uncontrolled anecdotal reports of improved wellbeing, energy levels and seizure control from the diet.

10.19 The Subcommittee noted evidence from a small study investigating the long-term effects of ketogenic diets on carnitine levels as assessed at 0, 1, 6, 12, and 24 months in 38 patients on a standard ketogenic diet (Berry-Kravis et al. Epilepsia. 2001;42:1445-51).

10.19.1 The Subcommittee noted that in this study, three patients had carnitine deficiency at baseline and received supplementation, carnitine decreased in the first few months of the diet and then generally stabilised in non-supplemented patients, and that 19% of patients were supplemented with levocarnitine. The Subcommittee noted that baseline carnitine status was associated with the number of antiepileptic drugs at diet initiation ($P<0.05$) and that no patients showed clinical signs of carnitine deficiency during dietary therapy.

10.19.2 The Subcommittee noted that in this study, at 1 month, some patients who did not receive levocarnitine supplementation had reduced carnitine levels and at 5 months there were mild reductions in carnitine levels for these patients, but no patients were symptomatic of carnitine deficiency. Members considered that most patients in this study were not carnitine deficient. Members considered that not all patients in this study become carnitine deficient, but that patients with borderline or low carnitine at the start of ketogenic diet therapy were at risk of carnitine deficiency while on the diet.

10.20 Members considered that, if levocarnitine was to be funded for this patient group, many patients would start supplementation when their total plasma carnitine level is at or slightly below the lower limit of the normal range (35 umol/L). The Subcommittee considered that the optimal threshold for commencement of carnitine supplementation in patients on therapeutic ketogenic diets was unclear, and members considered that a threshold beneath the lower limit of normal may be more appropriate (eg total carnitine <26 umol/L).

10.21 The Subcommittee noted that patients on therapeutic ketogenic diets who respond to this treatment may stay on the diet for 2 years, and considered that levocarnitine supplementation in these patients would not result in cost savings to the health system.

10.22 The Subcommittee considered that there was insufficient evidence to support the use of levocarnitine in patients on therapeutic ketogenic diets for intractable epilepsy, and there was a lack of clarity around which patients would benefit most, how many patients this would be per year nationally, and what funding criteria should apply. The

Subcommittee considered that it could review a resubmission, if received, that ideally would include an updated definition of the patient group (eg carnitine deficiency due to valproate use; symptomatic; specific agents discontinued) and an updated threshold for total plasma carnitine level (eg less than 26 umol/L), if appropriate, and evidence for use of levocarnitine in this defined patient group. Members considered that neurologists may be able to provide valuable input regarding these concerns.

10.23 The Subcommittee noted that PHARMAC had provided draft Special Authority criteria, and members considered that it would need to be revised to include any new information or evidence received at the time the funding application is reconsidered.

Metabolic indications: inborn errors of metabolism

10.24 The Subcommittee noted that inborn errors of metabolism are a heterogenous group of diseases that include the fatty acid oxidation disorders, which are caused by one or more genetic mutations that disrupt mitochondrial oxidation or fatty acid transport.

10.25 The Subcommittee noted that carnitine transport or uptake deficiencies such as systemic primary carnitine deficiency (CDSP) are sub-types of fatty acid oxidation disorders and that CDSP predominantly affect infants and children, causing death or irreversible organ damage if not treated early. The Subcommittee noted that patients with carnitine transport or uptake deficiencies cannot synthesise enough carnitine for essential requirements, and considered that these patients require levocarnitine to prevent damage from this disorder.

10.26 The Subcommittee noted that carnitine supplementation in fatty acid oxidation disorders (other than carnitine transport or uptake deficiencies) is debated, potentially offering benefit in secondary carnitine deficiency but in other cases may actually cause secondary carnitine deficiency due to conjugation of fatty acids with carnitine, which is then excreted.

10.27 The Subcommittee noted that PHARMAC has received NPPA applications for levocarnitine use in metabolic indications including fatty acid oxidation disorders and CDSP, with requested dosages ranging from 50 mg to 400 mg per kg per day, often in divided doses and adjusted to plasma carnitine level. The Subcommittee noted that for primary carnitine deficiency, patient age at the time of NPPA application ranged from <1 to 40 years, with average age of about 11 years.

10.28 The Subcommittee noted that PHARMAC staff have inferred from the NPPA data that the prevalence of primary carnitine deficiency (severe enough to warrant supplementation) is no greater than 1:250,000 in New Zealand, and that staff had estimated that an additional 5 patients with inborn errors of metabolism would require levocarnitine supplementation in any one year. Some members considered that the patient numbers may be an overestimate. Members noted that there a higher incidence of very long chain acyl Co-A dehydrogenase deficiency, a type of inborn error of metabolism, in Māori than in non-Māori in New Zealand.

10.29 The Subcommittee noted that this PHARMAC-initiated application meets the definition of a rare disorder as per the second of PHARMAC's Three Principles for Rare Disorders.

10.30 The Subcommittee noted there is limited evidence regarding levocarnitine for patients with inborn errors of metabolism, and that a 2012 Cochrane systematic review (Nasser et al. Cochrane Database Syst Rev. 2012; 2: CD006659) identified no clinical trials that met criteria for inclusion, thus reported no conclusions regarding carnitine supplementation for patients with inborn errors of metabolism.

10.30.1 The Subcommittee noted the following expert opinion review publications regarding treatment of carnitine deficiency due to inborn errors of metabolism:

- Merritt et al. Ann Transl Med. 2018:24;473
- Magoulas et al. Orphanet J Rare Dis. 2012:7;68
- El-Hattab et al. GeneReviews [Internet]. 2012 [updated 2016]

10.30.2 The Subcommittee considered that there are reports of improvement in metabolic decompensation and skeletal and cardiac muscle function after carnitine supplementation of patients with metabolic diseases. Members also considered that there are reports of patients with metabolic diseases who have discontinued carnitine supplementation and subsequently experienced hypoglycaemic attacks or sudden death from cardiac arrhythmia.

10.31 The Subcommittee considered that, while there is a lack of clinical trial evidence for carnitine supplementation and that the evidence of benefit remains uncertain, carnitine supplementation may benefit some individuals, and that in cases of CDSP carnitine supplementation should be commenced quickly to prevent harm. The Subcommittee considered that maintaining high carnitine levels in patients with CDSP was important to ensure availability for critical cell functions.

10.32 Members considered that for patients with inborn errors of metabolism other than CDSP, intermittent carnitine therapy commenced upon developing symptoms of carnitine deficiency or very low carnitine levels could control symptoms.

10.33 The Subcommittee considered that levocarnitine supplementation is generally well tolerated, noting that although there were a number of possible side effects (including diarrhoea, gastrointestinal motility, intestinal discomfort, and a fishy odour that is released in breath, sweat and urine due to production of trimethylamine) these were generally tolerated.

10.34 Members noted that only a small proportion (about 10%) of a 100 mg per kg oral daily dose is absorbed. Higher doses may need to be utilised in very unwell patients who are metabolically unstable.

10.35 The Subcommittee considered that treatment with levocarnitine for patients with inborn errors of metabolism may lead to stability of disease, which may result in cost savings to the health system.

11 Migalastat supplier update – Fabry disease

Application

11.1 The Subcommittee reviewed a resubmission from Amicus Therapeutics Pty Ltd for migalastat for the treatment of Fabry 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 migalastat be funded with a medium priority in the context of the rare disorders therapeutic area and possible funding of enzyme replacement therapy for Fabry disease, subject to the following Special Authority criteria:

Special Authority for Subsidy

Initial application – only from a relevant specialist. Approvals valid for 24 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; and
2. Patient must have an amenable *GLA* mutation (see Note below) confirmed by molecular genotyping performed in an accredited diagnostic laboratory; and
3. Either:
    - 3.1. Patient has renal disease as defined by 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 measurements, 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 glycosphingolipid deposition in the kidneys; or
    - 3.2. Patient has cardiac disease as defined by left ventricular hypertrophy (determined by MRI or ECG) and/or severe arrhythmia or conduction defect; or
    - 3.3. Patient has ischaemic vascular disease determined on objective measures; or
    - 3.4. Patient has uncontrolled chronic pain despite use of analgesic/antiepileptic medications; and
4. Patient must not have conditions related to Fabry disease which may compromise response to migalastat; and
5. Patient must not have another life threatening or severe disease where the prognosis is unlikely to be influenced by migalastat or might be reasonably expected to compromise a response to migalastat; and
6. Migalastat not to be used concomitantly with enzyme replacement therapy; and
7. Migalastat to be administered at doses no greater than 150 mg every other day.

Renewal – only from a relevant specialist. Approvals valid for 24 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 developed another life threatening or severe disease where the long-term prognosis is unlikely to be influenced by treatment with migalastat hydrochloride; and
3. Patient has not developed another medical condition that might reasonably be expected to compromise a response to migalastat hydrochloride.

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

Discussion

11.4 The Subcommittee noted that an application from Amicus for migalastat for the treatment of Fabry disease was considered by the Rare Disorders Subcommittee in November 2018. At that time, the Subcommittee recommended the application be declined based on insufficient evidence of long-term beneficial effects on morbidity and mortality. PTAC subsequently reviewed the Record of the November 2018 Rare

Disorders Subcommittee in February 2019 and agreed with the Subcommittee's recommendation to decline the application.

11.5 The Subcommittee noted that an application for agalsidase alfa for the treatment of Fabry disease was also considered by the Rare Disorders Subcommittee in November 2018. At that time, the Subcommittee recommended that agalsidase alfa be funded for the treatment of Fabry disease with a medium priority. The Subcommittee noted that PTAC subsequently declined the application for agalsidase alfa in February 2019 due to low quality evidence consistent with only modest clinically meaningful long-term health benefits.

11.6 The Subcommittee noted that applications for both agalsidase alfa and agalsidase beta for Fabry disease had been considered previously on several occasions by PTAC (agalsidase beta: May 2006, February 2009, November 2011; agalsidase alfa: February 2009, November 2011).

11.7 The Subcommittee noted that a resubmission from Amicus for migalastat was received by PHARMAC in August 2019, which addressed the following main areas of concern raised by the Rare Disorders Subcommittee and PTAC in their review of treatments for Fabry disease: uncertainty about disease severity and clinical need for treatment, long-term effectiveness of treatments for Fabry disease, selection of patients for treatment, and treatment costs.

11.8 The Subcommittee re-reviewed the aetiology and natural history of Fabry disease. The Subcommittee noted that there is a spectrum of phenotypes, ranging from the most common and severe classical phenotype to atypical forms such as renal or cardiac specific variants. The Subcommittee noted that the major clinical manifestations of classical Fabry disease include angiokeratomas, acroparesthesia, hypohidrosis, corneal and lenticular opacities, progressive renal dysfunction, and cardiovascular disease. The Subcommittee noted that the life expectancy of individuals with untreated classical Fabry disease is reduced by more than 20 years (average age of death 41 years; Mehta & Hughes. Fabry Disease. 2002 Aug 5 [Updated 2017 Jan 5]. In: Adam et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2019).

11.9 The Subcommittee noted that there is currently no specific treatment for Fabry disease funded in New Zealand; the current standard of care is based around the general management of renal impairment (including renal transplantation), vascular disease, cardiac manifestations, and pain.

11.10 The Subcommittee considered that, unlike ERT for Gaucher disease, treatments for Fabry disease aim to stabilise disease and prevent further decline, rather than significantly improve the disease course.

11.11 The Subcommittee noted that migalastat is a pharmacological chaperone that selectively and reversibly binds to and stabilises certain mutant forms of α-Galactosidase A, thereby facilitating the catabolism of globotriaosylceramide (GL-3) and related substrates. The Subcommittee noted that migalastat is only effective in individuals with an amenable GLA mutation, which is approximately 35% to 50% of patients diagnosed with Fabry disease.

11.12 The Subcommittee noted that migalastat is not currently approved by Medsafe for the treatment of Fabry disease, but that it has 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.

11.13 The Subcommittee noted that the resubmission provided data from the clinical development program for migalastat, including longer-term unpublished data from ATTRACT, FACETS, and their extension studies, and a number of Phase 2 trials.

11.14 The Subcommittee noted that the updated renal function data provided in the resubmission indicated that the annualised change in eGFR (using the Chronic Kidney Disease Epidemiology Collaboration) was 0.69 mL/min/1.73 m2/year in ERT-naïve patients receiving migalastat over an average of 3.4 years (FACETS extension), and was -1.08 mL/min/1.73 m2/year in ERT-switch patients after 4 years of treatment with migalastat (ATTRACT extension). The Subcommittee noted that long-term data from the Phase 2 trials showed an annualised change in eGFR of -0.67 mL/min/1.73 m2/year over an average of 8.2 years of treatment. The Subcommittee considered that the results described above indicate that treatment with migalastat stabilises renal function, and that these results are particularly significant given that the standard rate of decline in renal function for healthy individuals is 0.5 mL/min/1.73 m2/year.

11.15 The Subcommittee noted that data from the extension study of FACETS indicated a continued reduction in left ventricular mass index (LVMI) over 5 years of treatment with migalastat, and that this reduction was most pronounced in patients with left ventricular hypertrophy at baseline. Members noted that it remains unclear whether improvement in LVMI would be observed if cardiac fibrosis had already developed.

11.16 The Subcommittee noted that the resubmission provided by the supplier also identified two recent reviews and a consensus statement regarding the effectiveness of ERT in Fabry disease (Germain et al. Mol Genet Metab. 2019;19:100454; Germain et al. Mol Genet Metab. 2019;126:224-235; Wanner et al. Mol Genet Metab. 2018;124:189-203). The Subcommittee considered that while these publications do not include mention of migalastat, the evidence indicate that ERT significantly improve long-term outcomes for patients with Fabry disease. The Subcommittee considered that these publications support its previous positive recommendation for agalsidase alfa (fund with a medium priority - November 2018).

11.17 The Subcommittee considered that ERT is the current standard of care in many countries for Fabry disease, and that it is therefore unlikely that extensive contemporary data describing the natural history of un-treated Fabry disease will ever be available.

11.18 The Subcommittee considered that migalastat is only effective in approximately 35% to 50% of patients with Fabry disease, and as such, funding only this agent would be inequitable to patients with Fabry disease without an amenable mutation. However, the Subcommittee noted that the resubmission from Amicus was suggesting that both ERT and migalastat should be funded for the treatment of Fabry disease, with migalastat likely to be the more suitable treatment option for patients with amenable GLA mutations due to its oral administration (vs. intravenous administration for ERT) and a potentially reduced risk of anti-drug antibody formation. The Subcommittee agreed that migalastat should only be considered for funding in the context of ERT potentially being funded for Fabry disease.

11.19 The Subcommittee considered that the prevalence of Fabry disease in New Zealand remains unclear, with estimates ranging from 1 in 60,000 to 1 in 117,000 live births. Members considered a personal communication about the latest data from the National Referral Laboratory in Australia that indicated prevalence is as high as 1 in 20,000, which would correlate to approximately 245 patients with Fabry disease in New Zealand. Members considered that the prevalence could vary significantly based on the identification of large affected families.

11.20 The Subcommittee noted that the supplier used an estimated prevalence of Fabry disease of 1 in 60,000 to calculate that there would be 7 patients eligible for migalastat in Year 1, increasing to 13 patients by Year 5. The Subcommittee considered that the recent Australian prevalence data from the National Referral Laboratory noted above suggests that there would be likely to be significantly more patients who may be eligible for migalastat than the supplier has estimated.

11.21 The Subcommittee considered that if migalastat or ERT were funded for the treatment of Fabry disease, that it would be important for patients to be included in a registry in order for New Zealand specific data to be collected, and to help evidence development internationally.

11.22 The Subcommittee considered that patients receiving Fabry-specific treatments would still require concomitant medications such as antihypertensives, statins, angiotensin-converting-enzyme inhibitors, and angiotensin II receptor blockers.

11.23 The Subcommittee considered that the cost effectiveness of migalastat at the proposed price is poor, but that the supplier has indicated that the price can be discussed further with PHARMAC. The Subcommittee considered that, based on the clinical evidence indicating that migalastat is non-inferior to ERT, the price of migalastat should be cost neutral to the price of ERT. The Subcommittee considered that migalastat should be included alongside ERT in any competitive procurement process that PHARMAC may undertake in the future for Fabry disease.

11.24 The Subcommittee considered that the updated evidence provided in the resubmission indicates that treatment with migalastat results in long-term stabilisation of renal and cardiac function in patients with Fabry Disease, and that this evidence was sufficient to support a positive recommendation for migalastat in the context of also recommending the funding of ERT.

11.25 The Subcommittee considered the proposed Special Authority criteria and advised that the initial period of approval should be longer than 12 months as it is unlikely a therapeutic response would occur sooner that 24 months, given that the aim of treatment would be to reduce the rate of decline in renal function or reduce the cardiac hypertrophy.