Record of the Rare Disorders Advisory Committee Meeting held online on 29 May 2024

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

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

The Rare Disorders Advisory Committee may:

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

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

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

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

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

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

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

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1. Attendance

Present
Rhiannon Braund – Chair
Adibah Khan
Emma Glamuzina
Helen Evans
James Cleland
Katherine Neas
Tim Stokes

Apologies
Carlo Marra

2. Summary of recommendations

Pharmaceutical and Indication	Recommendation
• Lanadelumab for routine prevention of recurrent attacks of hereditary angioedema, within the context of treatments for rare disorders, subject to Special Authority criteria	High Priority
• Belzutifan for the treatment of Von-Hippel Lindau disease within the context of treatments for rare disorders, subject to Special Authority criteria	Medium Priority
• Agalsidsase beta for Fabry within the context of treatments for rare disorders, subject to Special Authority criteria	High Priority
• Avalglucosidase alfa for the treatment of infantile onset Pompe disease within the context of treatments for rare disorders subject to Special Authority criteria	Medium Priority
• Avalglucosidase alfa for the treatment of late onset Pompe within the context of treatments for rare disorders, subject to Special Authority criteria	Medium Priority

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

3.1. This meeting record of the Rare Disorders Advisory Committee is published in accordance with the Terms of Reference for the Pharmacology and Therapeutics Advisory Committee (PTAC) 2021 and Specialist Advisory Committees 2021.Terms of

Reference describe, *inter alia*, the establishment, activities, considerations, advice, and the publication of such advice of Specialist Advisory Committees and PTAC.

3.2. Conflicts of Interest are described and managed in accordance with section 6.4 of the SAC Terms of Reference.

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

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

4. Welcome and introduction

4.1. The Chair welcomed the Committee with a karakia followed by whakawhanaungatanga.

4.2. The Chair noted that due to a Committee member being unwell that day, eliglutstat for the treatment of Gaucher disease would be reviewed by the Committee later at an ad-hoc meeting.

5. Record of the Rare Disorders Advisory Committee meeting held Tuesday 7 March 2023

5.1. The Committee reviewed the minutes of the Rare Disorders Advisory Committee meeting held on Tuesday 7 March 2023, and agreed that the minutes be accepted.

6. Therapeutic Group Review

6.1. The Committee noted that the following applications that it had considered previously have since been ranked on one of Pharmac's relevant priority lists for funding applications:

6.1.1. SMA treatments (nusinersen and risdiplam) for spinal muscular atrophy type IV (aged 19 years and over at symptom onset), ranked on the Recommended for Decline list.

6.1.2. Teduglutide for short bowel syndrome intestinal failure (adults), ranked on the Options for Investment list.

6.2. The Committee noted that treatments for Fabry disease (agalsidase alfa and migalastat) and elosulfase alfa for mucopholysaccharidosis type IVA were currently under assessment after receiving positive funding recommendations at the Committee's last meeting in 2023.

6.3. The Committee noted that Pharmac is currently reviewing consultation feedback on a proposal to decline the following funding applications, following recommendations to decline at previous meetings of the Committee:

6.3.1. Alglucosidase alfa for late-onset Pompe disease. The Committee noted this medicine is planned to be discontinued globally, however an application for avalglucosidase alfa is being considered by the Committee at this meeting.

6.3.2. Miglustat for Gaucher disease.

6.3.3. Miglustat for Niemann Pick Type C.

6.4. The Committee noted that Pharmac is currently reviewing consultation feedback on a proposal to decline sapropterin for hyperphenylalaninemia due to PKU in PKU patients who are not pregnant. The Committee noted that this application has been superseded by a separate funding application for all patients with PKU.

6.5. The Committee noted that a funding application for nitisinone for tyrosinaemia type 1 is currently ranked on the Options for Investment list. The Committee noted that Pharmac has approved funding for nitisinone for individual named patients with this indication via the Named Patient Pharmaceutical Assessment (NPPA) pathway. Members considered it would be appropriate to list on the Pharmaceutical Schedule and considered the Annual Tender process to be an appropriate competitive process to seek bids for supply.

Updates to funding for rare disorders' medicines

6.6. The Committee noted that in May 2024, trientine hydrochloride capsules for the treatment Wilson disease was listed in the Pharmaceutical Schedule, subject to eligibility criteria.

6.7. The Committee noted that in February 2024, a range of supplements for PKU and other inherited metabolic diseases were listed in the Pharmaceutical Schedule, subject to eligibility criteria. The Committee noted that work is ongoing to widen the range of funded supplements, but no decision had yet been made.

6.8. The Committee noted in May 2023, risdiplam (brand name Evrysdi) for spinal muscular atrophy was listed in the Pharmaceutical Schedule, subject to eligibility criteria. The Committee noted this provided an oral option for people with SMA, in addition to intrathecally administered nusinersen (Spinraza), which was funded from January 2023.

Therapies for rare disorders being reviewed by other Committees

6.9. The Committee noted a funding application for eculizumab for atypical haemolytic uremic syndrome (aHUS) was recommended for funding with a low priority, within the context of treatments for renal disease, by the Nephrology Advisory Committee in March 2023. The Committee noted there remained uncertainties on comparator treatments and Pharmac staff may seek further advice.

6.10. The Committee noted a funding application for voretigene neparvove for inherited retinal dystrophy was deferred by PTAC in February 2023. The Committee noted that additional information had been submitted by the supplier and a clinician, which will be reviewed by PTAC and/or the Ophthalmology Advisory Committee soon.

6.11. The Committee noted Pharmac had received a funding application for burosumab for X-linked hypophosphatemia and intended to seek advice from the Endocrinology Advisory Committee at a future meeting.

NPPA review

6.12. The Committee noted an overview from Pharmac staff about NPPA applications for individuals with rare disorders. NPPA provides a more flexible pathway to consider the funding of medicines for individuals who have exceptional circumstances. Members considered that reviewing the types of applications that had been made was useful for

identifying potential medicines that could be considered for listing in the Pharmaceutical Schedule.

6.13. The Committee considered NPPA is a useful pathway in the context of rare disorders, noting that New Zealand does not have alternative funding pathways for rare disorder medicines such as the Life Saving Drugs Program in Australia.

6.14. The Committee noted Pharmac staff intended to review treatments that have been funded via NPPA and could be moved to the Pharmaceutical Schedule. Members considered there would be suitable candidates for this work from the rare disorders treatments portfolio, for example nitisinone, empagliflozin (for glycogen storage disease type 1b) and biotin.

6.15. The Committee noted applications for continuous glucose monitors (CGMs) for rare glycogen storage diseases had been approved via NPPA. The Committee noted Pharmac had consulted on a proposal to fund continuous glucose monitors (CGMs) for type 1 diabetes in March 2024, and considered funding for these disorders could be moved from NPPA to the Pharmaceutical Schedule as part of any decision for funding of CGMs. The Committee noted Pharmac intended to seek further advice from the Diabetes Advisory Committee on CGMs and would consider access for those groups.

Horizon scanning

6.16. The Committee noted there is developing evidence for the use of eculizumab for myasthenia gravis. The Committee noted eculizumab had not received Medsafe approval for this indication, however had been approved overseas. Members considered it would be a useful treatment to consider in the New Zealand context.

6.17. The Committee noted a new class of treatments for immune-based neurological diseases called FcRn inhibitors (for example efgartigimod) that have signalled good efficacy in clinical trials. The Committee noted this is an infusion-based medicine. Members considered it would be likely that Pharmac would soon begin receiving NPPA applications for these medicines.

6.18. The Committee noted the use of IBAT inhibitors internationally for paediatric forms of inherited liver diseases. The Committee considered these are becoming the standard of care, however, are not currently Medsafe approved. The Committee noted these could have substantial benefits for New Zealand patients and avoid the need for liver transplantation. Members noted there is also emerging data for use in adults, which could create a significantly larger market. Members considered that funding applications would likely be made to Pharmac in the future, likely through the NPPA pathway initially.

6.19. The Committee noted emerging evidence for vutrisiran for cardiac amyloidosis. The Committee noted a funding application for tafamidis for cardiac amyloidosis was currently under assessment by Pharmac staff. The Committee considered vutrisiran was likely to be more effective than tafamidis in this indication and requested Pharmac staff seek a funding application for this agent.

6.20. The Committee noted precision therapy is a rapidly developing area of research and development. The Committee considered that New Zealand would need to develop a national pathway for genetic testing to identify patients eligible for treatments such as gene therapy. Members considered it is currently unclear who is responsible for developing this pathway, and cross-agency work would be required to successfully implement this. The Committee considered there would be value in establishing a genomics advisory group within Pharmac to provide advice on the strategic implementation of funding for gene therapies, provide advice on the ethics of gene therapy and testing across ethnic groups, particularly Māori, and ensuring equity of access to diagnosis and extremely expensive treatments.

6.21. The Committee also considered it would be useful, as part of any cross-agency work, to develop a framework for consideration and funding of very high cost medicines for rare disorders. The Committee noted that funding of medicines for rare disorders was currently undertaken using Pharmac's Factors for Consideration.

Rare disease strategy

6.22. The Committee noted the Ministry of Health is currently developing a rare disorders strategy. The Committee noted Pharmac had provided input into this strategy, particularly on strategies for pharmaceuticals.

7. Lanadelumab for routine prevention of recurrent attacks of hereditary angioedema

Application

7.1. The Advisory Committee reviewed the application for lanadelumab for routine prevention of recurrent attacks of hereditary angioedema (HAE).

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

Recommendation

7.3. The Advisory Committee **recommended** that lanadelumab be funded for routine prevention of recurrent attacks of hereditary angioedema with a **high priority**, within the context of treatments for rare disorders, subject to the following Special Authority criteria:

> **Initial application - (hereditary angioedema)** from a clinical immunologist or specialist allergist, or any relevant practitioner under the recommendation of a clinical immunologist or specialist allergist. Approvals valid for 12 months for applications meeting the following criteria:
> All of the following:
> 1. Patient has chronic hereditary angioedema (HAE) type 1 or type 2; and
> 2. Either:
> 3.1 Patient is receiving routine prophylaxis for HAE with a C1 esterase inhibitor at the time of application; or
> 3.2 Patient has experienced at least 12 treated acute HAE attacks, defined as those of a severity necessitating immediate medical intervention with either icatibant or C1-esterase inhibitor concentrate, within the previous six months; and
> 3. Treatment is not in combination with routine C1-esterase inhibitor concentrate.
>
> **Renewal - (hereditary angioedema)** - from any relevant practitioner. Approvals valid for 12 months for applications meeting the following criteria:
> All of the following:
> 1. Patient has experienced, and continues to experience, an adequate response to treatment, defined as a reduction in the baseline number of attacks of a severity necessitating medical intervention with either icatibant or C1-esterase inhibitor; and
> 2. Treatment is not in combination with a C1-esterase inhibitor concentrate

7.4. In making this recommendation, the Advisory Committee considered:

- people with HAE who require prophylactic treatment for attacks are currently experiencing unmet health need in New Zealand
- the available evidence indicates lanadelumab lowers the incidence of HAE attacks, decreases severity or breakthrough attacks, increases quality of life, and does not increase the risk of adverse events
- compared with intravenous C1-esterase inhibitor (C1-INH), lanadelumab would provide superior suitability due to not requiring infusion time and other requirements from infusion services

- further advice from specialists in immunology and/or the NZ Blood Service (NZBS) may be required to understand how treatment with lanadelumab may replace C1-INH treatment in the New Zealand setting, the number of people receiving intravenous vs subcutaneous C1-INH, the appropriateness of treating people under 12 years of age with lanadelumab, and the duration of treatment with lanadelumab for the prevention of HAE attacks.

Discussion

Māori impact

7.5. The Committee discussed the impact of funding lanadelumab for the prevention of HAE attacks on Māori health outcomes. The Committee noted HAE is not one of Pharmac's five Hauora Arotahi - Māori Health Areas of Focus. The Committee considered that although there is no evidence to suggest HAE is more prevalent in Māori, this does not exclude the possibility that Māori with HAE experience inequitable access to specialist services and/or inequitable health outcomes.

Impact on Pacific peoples, disabled people, tāngata whaikaha Māori, and other people who have been underserved by the health system

7.6. The Committee discussed the impact of funding lanadelumab for the prevention of HAE attacks on people who have been underserved by the health system. The Committee did not identify any group with known inequitable health outcomes associated with HAE but noted that the lack of available evidence did not exclude the possible presence of these inequities.

Background

7.7. The Committee noted that in September 2015, Pharmac announced the decision to list icatibant (Firazyr) in the Pharmaceutical Schedule for the treatment of acute attacks of hereditary angioedema (HAE).

7.8. The Committee noted that Pharmac does not currently list any treatments on the Pharmaceutical Schedule for prophylaxis of HAE attacks. The Committee noted that applications to New Zealand Blood Service (NZBS) can be made for intravenous C1-INH concentrate for people who require prophylaxis of HAE attacks.

Health need

7.9. The Committee noted that HAE is a chronic condition caused by either a deficiency of C1 inhibitor (C1INH) protein (Type 1) or dysfunction of C1INH (Type 2). The Committee noted that HAE is a lifelong condition with symptoms often beginning in early childhood, although diagnosis may be delayed for many years (Aygoren-Pursun et al. Patient Prefer Adherence. 2016;10:1699-77). The Committee considered that delayed diagnosis increased the risk of death from laryngeal attacks, prescribing of treatments that would otherwise be unnecessary, and abdominal surgery that would otherwise be unnecessary for people with HAE.

7.10. The Committee noted in the 2019 national audit of HAE and acquired angioedema (AAE) in New Zealand (Lindsay et al. Intern Med J. 2022;52:2124-9) it was reported that 54 people are known to have received treatment in New Zealand in the years 2015 to 2019; of these people, 51 were diagnosed with HAE by a clinical immunologist, equating to a crude prevalence of known HAE in New Zealand of 1 in 100,000. The Committee noted that internationally the exact prevalence of HAE is unknown, but current published estimates range from 1 per 10,000 to 1 per 150,000 persons, with several sources agreeing 1 per 50,000 likely to be the closest estimate (Roche et al. Ann Allergy Asthma Immunol. 2005;94:498-503, Bygum. Br J Dermatol.

2009;161:1153-8, Lei et al. Asian Pac J Allergy Immunol. 2011;29:327-31, Lumry. Am J Manag Care. 2013;19:s103-10, Nordenfelt et al. Allergy Asthma Proc. 2014;35:185-90).

7.11. The Committee noted that HAE manifests clinically as unpredictable, intermittent attacks of subcutaneous or submucosal oedema of the face, larynx, gastrointestinal tract, limbs and/or genitalia (Zuraw. N Engl J Med. 2008;359:1027-36). The Committee considered that HAE is associated with morbidity and mortality, noting that approximately 50% of all people with HAE will experience a laryngeal attack in their lifetime, and there is no way to predict who is at risk of a laryngeal attack, which can be potentially life-threatening due to the risk of asphyxiation (Bork et al. Arch Intern Med. 2003;163:1229-35, Bork et al. Am J Med. 2006;119:267-74).

7.12. The Committee considered that HAE attacks can negatively affect the quality of life of people with HAE, and noted people with HAE have reported lower productivity, missed time from work or school, and potentially missed career and educational opportunities (Lumry et al. Allergy Asthma Proc. 2010;31:407-14, Wilson et al. Ann Allergy Asthma Immunol. 2010;104:314-20, Bernstein. Allergy Asthma Proc. 2013;34:3-6, Aygören-Pürsün et al. Orphanet J Rare Dis. 2014;9:99, Nordenfelt et al. Allergy Asthma Proc. 2014;35:185-90). The Committee noted many people with HAE experience a significant psychological burden, including anxiety and depression (Huang. Allergy Asthma Proc. 2004;25:127-31, Banerji. Ann Alergy Asthma Immunol. 2013;111:329-36, Caballero et al. Allergy Asthma Proc. 2014;35:47-53, Bygum et al. Acta Derm Venereol. 2015;95:706-10), which may be caused by the unpredictability of HAE attacks and the fear of pain and asphyxiation (Lumry et al. Allergy Asthma Proc. 2014;35:371-6). The Committee considered the quality of life for people who care for people with HAE may also be negatively affected by the condition.

7.13. The Committee noted HAE does not fall into one of Pharmac's Hauora Arotahi (Māori Health Areas of Focus). The Committee noted that recent national audit of HAE in New Zealand interviewed 38 people (out of the 51 people identified with HAE) with HAE who were recruited via clinical immunologists and the New Zealand Blood Service, three of whom identified as Māori (Lindsay et al. Intern Med J. 2022;52:2124-9). The Committee considered the rarity of HAE probably explained both the lack of data on Māori health outcomes and the uncertainty as to whether the disease disproportionately affects population groups already be experiencing health inequity.

7.14. The Committee noted the currently available treatments for short and long-term prophylaxis of HAE attacks in New Zealand. Stanozolol (a synthetic steroid that is derived from testosterone and has anabolic and androgenic properties) is available but requires a Named Patient Pharmaceutical Assessment (NPPA) application. The Committee considered stanozolol, as an anabolic steroid, is associated with a wide range of adverse effects including cardiotoxicity, hepatotoxicity, and effects on both the male and female reproductive systems. Tranexamic acid is funded and used in children and those with acquired C1-INH deficiency, however the Committee considered that there is very limited evidence showing benefit of tranexamic acid for HAE. The Committee noted that C1-INH concentrate is available as both intravenous (IV) and subcutaneous (SC) formulations, for either short or as long-term prophylaxis, through an application to the NZBS.

7.15. The Committee noted that the 2021 international World Allergy Organisation/European Academy of Allergy & Clinical Immunology (WAO/EAACI) guidelines for the management of HAE recommended lanadelumab as an appropriate option for the first-line treatment for prophylaxis of HAE attacks, alongside C1-INH and Berotralstat (Maurer et al. Allergy. 2022;77:1961-90). The Committee noted the guidelines state there is not currently enough evidence to recommend any of the three treatments over the others. The Committee noted that androgens (eg stanozolol) were recommended

in the guideline to only be used as second line prophylaxis due to numerous side-effects, and surveillance requirements. The Committee considered that treatment for prophylaxis of HAE attacks in New Zealand is not in line with international guidelines.

7.16. The Committee noted consumer feedback received as part of the submission for lanadelumab from HAE Australasia. The Committee noted consumers' reports of the negative impacts on health and quality of life caused by HAE attacks. The Committee also noted consumer feedback on how HAE attack prophylaxis with lanadelumab has improved their quality of life and ability to participate in work and life activities.

7.17. The Committee considered people with HAE who require prophylactic treatment for attacks are currently experiencing unmet health need in New Zealand.

Health benefit

7.18. The Committee noted that lanadelumab is a fully human, monoclonal antibody which inhibits active plasma kallikrein proteolytic activity without binding prekallikrein, the inactive precursor found in the circulation. The Committee noted that increased plasma kallikrein activity leads to angioedema attacks in patients with HAE. The Committee noted that control of plasma kallikrein activity is the mechanism by which lanadelumab decreases HAE attacks (Medsafe datasheet).

7.19. The Committee noted the HELP phase 3, international, randomised, double-blind, parallel-group, placebo-controlled trial and its associated extension trial provided the key primary evidence for lanadelumab for the prevention of HAE attacks (Banjeri et al. JAMA. 2018;320:2108-21, Riedl et al. Allergy. 2020;75:2879-87).

7.19.1. Participants received 26-week treatment with subcutaneous lanadelumab 150 mg every 4 weeks ($n = 28$), 300 mg every 4 weeks ($n = 29$), 300 mg every 2 weeks ($n = 27$), or placebo ($n = 41$). The Committee noted the study was powered to compare effects of lanadelumab vs placebo but was not designed or powered to compare the effects of the three lanadelumab groups.

7.19.2. Over the 26 weeks, a significantly greater proportion participants in all lanadelumab treatment groups were attack free (39.3% in the 150-mg every-4-week group; $P < .001$; 31.0% in the 300-mg every-4-week group; $P = .001$; and 44.4% in the 300-mg every-2-week group; $P < .001$) compared with placebo (2.4%), and reductions of 70% or more and 90% or more were observed in 75.9% to 88.9% and 55.2% to 66.7% of patients treated with lanadelumab ($P < .001$ for all) compared with 9.8% and 4.9% of patients in the placebo group, respectively. The Committee noted treatment with lanadelumab for 26 weeks significantly reduced the mean attack rate (0.26-0.53 attacks/month) compared with placebo (1.97 attacks/month).

7.19.3. The Committee considered the findings from the trial supported the use of lanadelumab for the prevention of HAE attacks. The Committee noted participants experienced a significant improvement in quality-of-life total scores over 26 weeks in all lanadelumab treatment groups compared with placebo.

7.20. The Committee noted most adverse events reported in the HELP trial (98.5%) were mild to moderate in severity. The Committee noted the most reported treatment-emergent adverse events in people treated with lanadelumab that were considered related to treatment were injection site pain (41.7%), injection site erythema (9.5%), injection site bruising (6.0%), and headache (7.1%); there were no deaths or related serious treatment-emergent adverse events.

7.21. The Committee noted results from the Cochrane systematic review of randomised controlled trials in children or adults with HAE that used medications to prevent HAE attacks (*N* = 912 across 15 studies) (Beard et al. Cochrane Database Syst Rev. 2022;11:CD013403). The Committee noted the review concluded that the available data suggests berotralstat, C1-INH, danazol and lanadelumab are effective in lowering the risk or incidence (or both) of HAE attacks, and that C1-INH and lanadelumab also decrease the severity of breakthrough attacks (data for other treatments were not available). The Committee noted that review reported avoralstat, berotralstat, C1-INH, and lanadelumab improve quality of life and do not increase the risk of adverse events, including serious adverse events. The Committee noted the review reported it is possible that subcutaneous C1-INH and recombinant human C1-INH are more effective than berotralstat and lanadelumab in reducing the risk of breakthrough attacks, but noted the small number of studies and small size of the studies meant the certainty of the evidence was low, and that, along with the lack of head-to-head trials prevented the authors from drawing firm conclusions on the relative efficacy of the treatments.

7.22. The Committee noted results of an indirect treatment comparison cohort study that combined data from the HELP study with the CHANGE study (a 12-week parallel arm crossover study that assessed intravenous (IV) C1-INH) to compare the lanadelumab to IV C1-INH using Bayesian and frequentist analyses (Mendivil et al. Drugs R D. 2021;21:113-21). The Committee noted both Bayesian and frequentist analyses suggested that lanadelumab reduced HAE attack rate by 46–73% versus intravenous C1-INH, risk of first attack after day 0 was comparable between intravenous C1-INH and both lanadelumab doses, and risk of first attack after day 70 was reduced by 81-83% with lanadelumab 300 mg every 2 weeks, compared with C1-INH. The Committee noted the authors concluded findings from the two methodologies supported favourable efficacy of lanadelumab in reducing the HAE attack rate and extending attack-free intervals for people with HAE.

7.23. The Committee considered the available evidence indicated lanadelumab lowers the incidence of HAE attacks, decreases severity or breakthrough attacks, increases quality of life, and does not increase the risk of adverse events. The Committee considered the evidence of good quality (phase 3, randomised trial) in the context of rare disorders, but noted its potential for imprecision due to the limited number and size of clinical trials. The Committee considered there was no evidence for differing efficacy between 2-weekly and 4-weekly lanadelumab, noting the HELP trial was not powered to assess these differences.

Suitability

7.24. The Committee noted that lanadelumab is administered via subcutaneous injection with a maximum dose of two injections per month. The Committee considered that compared with intravenous C1-INH, lanadelumab would provide superior suitability due to not requiring infusion time and other requirements of infusion services. The Committee considered this suitability benefit less relevant in comparison to subcutaneous C1-INH but did not have any information available on the proportions of people receiving IV vs subcutaneous C1-INH in the New Zealand setting.

Cost and savings

7.25. The Committee considered the duration of lanadelumab treatment for prevention of HAE attacks was unclear from the available evidence. The Committee considered it could be assumed the condition would be unlikely to remit, and that lifelong therapy is likely to be required.

7.26. The Committee considered further advice from specialists in immunology and/or the NZ Blood Service may be required to understand how treatment with lanadelumab may replace C1-INH treatment in the New Zealand setting, the number of people receiving IV vs subcutaneous C1-INH, the appropriateness of treating people under 12 years of age with lanadelumab, and the duration of treatment with lanadelumab for the prevention of HAE attacks.

Funding criteria

7.27. The Committee noted that in Australia, lanadelumab has been recommended by the PBAC for people who have experienced at least 12 treated acute attacks of HAE within a 6-month period prior to treatment, and NICE in England/Wales recommended lanadelumab for people having two or more clinically significant attacks per week over 8 weeks. The Committee considered it reasonable for Pharmac to align funding criteria with these international recommendations.

Summary for assessment

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

Population	People with HAE who require prophylactic treatment for the ongoing prevention of angioedema attacks, and have had at least twelve treated acute HAE attacks within the previous six months. Note: Qualifying attacks are to be documented as having required acute treatment.
Intervention	Lanadelumab • Initial dose of 300mg every two weeks, administered via subcutaneous injection. • Those who experience attack-freedom may reduce the dosing frequency to four-weekly. In an HAE attack occurs, treatment with icatibant or C1-INH.
Comparator(s) (NZ context)	Potential comparators include: • No prophylactic treatment • C1-INH IV for prophylaxis if suitable (requires application to the NZBS) (500 IU per vial at a strength of 50 IU/mL, recommended dosage 20 IU per kg of bodyweight, administered intravenously) • C1-INH SC (requires application to the NZBS) (60 IU per kg of bodyweight twice weekly) If an HAE attack occurs, acute treatment with icatibant or C1-INH.
Outcome(s)	Reduction in rate of HAE attacks, resulting in improved HRQoL, and reduction in use of ODT. • Lanadelumab was associated with a reduction in the frequency of acute angioedema attacks compared to placebo (percentage reduction -87% [95% CI, -76% to -93%]) (Benerji et al. JAMA. 2018;320:2108-21)
Table definitions: **P**opulation: The target population for the pharmaceutical, including any population defining characteristics (eg line of therapy, disease subgroup) **I**ntervention: Details of the intervention pharmaceutical (dose, frequency, treatment duration/conditions for treatment cessation).	

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

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

8. Belzutifan for Von Hippel-Lindau (VHL) disease

Application

8.1. The Advisory Committee reviewed the application for belzutifan for the treatment of von- Hippel Lindau

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

Recommendation

8.3. The Advisory Committee **recommended** that belzutifan for the treatment of Von-Hippel Lindau disease be recommended with a **medium** priority within the context of treatments for rare disorders, subject to the following Special Authority criteria:

> **Initial application** – (**von Hippel-Lindau disease**) from a medical oncologist**.** Approvals valid for 12 months for applications meeting the following criteria:
>
> All of the following:
>
> 1. Patient has a confirmed diagnosis of von Hippel-Lindau disease; and
> 2. Patient has associated renal cell carcinoma, central nervous system haemangioblastoma, or pancreatic neuroendocrine tumours; and
> 3. There are no RCC lesions ≥3 cm that require immediate surgical intervention; and.
> 4. There is no evidence of metastatic disease; and
> 5. Patient has an ECOG performance status of 0 or 1.
> 6. Patient has not received any prior systemic anti cancer therapy
>
> **Renewal application** – (**von Hippel-Lindau disease**) from a medical oncologist**.** Approvals valid for 12 months for applications meeting the following criteria:
>
> All of the following:
>
> 1. The patient has not experienced clinical progression; and
> 2. Either:
>
> 2.1. The patient has not experienced radiological progression; or
>
> 2.2. The patient has experienced radiological progression but is not experiencing clinical progression and the treating clinician assesses the patient is still deriving clinical benefit.

8.4. The Advisory Committee based its recommendation on the following:

- Belzutifan treatment is less invasive than surgical options with a decreased risk of end organ function loss
- Evidence from low quality data that belzutifan may reduce tumour size markedly and delay time to surgery, based on the results of one phase II single-arm clinical study (LITESPARK-004).
- The immaturity of the published data, and lack of long term follow up data.

8.5. The Advisory Committee recommended the Cancer Treatments Advisory Committee review the application and the recommended Special Authority criteria.

Discussion

Patient lived experience

8.6. A person living with Von-Hippel Lindau (VHL) disease shared their experience with the Rare Disorders Advisory Committee and Pharmac staff. The Committee and Pharmac

staff valued this opportunity and considered that a different perspective helped to frame the Committee's discussions.

8.7. The individual is a member of the VHL Alliance in New Zealand, who advocate for individuals with VHL and help them to navigate the health system.

8.8. They detailed that VHL is not curable, variable in presentation between different individuals and something that people have to manage throughout their lifetimes.

8.9. They shared that the type of VHL depends on how many specialists you see, their own experience being seeing up to 10 different specialists.

8.10. They described the personal burden felt by people needing to be highly health literate through understanding the surveillance guidelines and surgical interventions that are available and working with each of the specialists. They said it was rare that specialists work together to manage the disease and the burden fell to the individual to manage their care.

8.11. They recounted their own challenging care journey, with the need to navigate multiple specialists, as well as system lapses where they were not adequately referred or reassessed. They highlighted the need to be a 'powerful patient' to drive their own care through understanding guidelines, when and how often scans should happen, and what treatment options are available.

8.12. The individual viewed the potential funding of belzutifan as an opportunity for one single specialist to be able to manage their condition. They hoped this would result in less appointments, scans, time spent in hospital and less time for people to help them get to and from hospital for the different specialists, with a more consistent care approach and less misunderstanding when otherwise dealing with more than one specialist in what is a complex syndrome.

8.13. They acknowledged that treatment with belzutian would require a lifetime of treatment, and that there were adverse effects associated with it including fatigue and anaemia.

8.14. They described how they anticipated belzutian would positively change the life of the person with VHL and how the disease was managed, reducing the burden of disease surveillance, appointments, and time spent in hospital away from whānau.

Māori impact

8.15. The Committee discussed the impact of funding belzutifan for the treatment of VHL disease on Pharmac's Hauroa Arotahi: Māori health areas of focus and Māori health outcomes. The Committee considered that while there was a lack of data for the impacts of VHL disease on Māori, in general terms Māori have received fewer referrals, fewer diagnostic tests and less effective treatment plans from their doctors compared to non-Māori (BPAC, Improving Māori health 2008). The Committee noted a 2021 report that reported hospital appointments are not accessible for more Māori adults than non-Māori adults and specialist appointments have unacceptably long wait times and occur less frequently for Māori (A Window On The Quality Of Aotearoa New Zealand's Health Care 2019, Health Quality and Safety Commission New Zealand).

8.16. The Committee considered the use of belzutifan may simplify the treatment and surveillance pathway for individuals with VHL which given the aforementioned accessibility issues for Māori adults may improve overall outcomes.

Impact on Pacific peoples, disabled people, tāngata whaikaha Māori, and other people who have been underserved by the health system

8.17. The Committee considered that while there was a lack of data for the impacts of VHL disease on people who have been underserved by the health system. The Committee

considered that in general Pacific peoples may experience similar barriers to healthcare as Māori. The Committee considered individuals with cancers are treated by multidisciplinary teams and have needed to self-advocate to progress their treatments. The Committee considered this requires an advanced level of health literacy which can be a barrier to equitable care, particularly for people underserved by the health system.

8.18. The Committee considered the use of belzutifan may provide some continuity of treatment and may improve outcomes for Pacific peoples and individuals underserved by the health system.

Background

8.19. The Committee noted that funding applications for belzutifan for any condition have not been previously considered, nor have any treatments for VHL disease.

8.20. The Committee noted that several Named Patient Pharmaceutical Assessment (NPPA) applications have been reviewed by Pharmac for belzutifan for VHL disease.

8.21. The Committee noted it had received a statement from an individual with VHL disease outlining their journey with VHL disease and experiences with the healthcare system.

Health need

8.22. The Committee noted VHL disease is an autosomal dominant inherited neoplastic disorder that demonstrates marked phenotypic variability and age-dependent penetrance. Tumours can arise in multiple organs and may become metastatic. The most frequent tumours are retinal and central nervous system haemangioblastomas, clear cell renal cell carcinoma (RCC), phaeochromocytoma, pancreatic islet tumours and endolymphatic sac tumours (ELSTs) (Maher et al. Eur J Hum Genet. 2011; 19: 617–23).

8.23. The Committee noted the VHL protein (pVHL) plays a role in regulating the proteolytic degradation of the α subunits of the HIF-1 and HIF-2 transcription factors. If pVHL is absent or inactive, HIF-1 and HIF-2 are stabilised and activate the hypoxic gene response implicated in diverse processes such as angiogenesis, proliferation, apoptosis, and metabolism (eg, VEGF, PDGFβ, TGFα, Cyclin D1 etc) (Maher et al. 2011).

8.24. The Committee noted if there is a confirmed family history of VHL disease, a diagnosis of VHL disease can be made by finding a single VHL tumour in an at risk relative. Clinical diagnosis of VHL disease without a positive family history requires the presence of two tumours (eg, two haemangioblastomas, or a haemangioblastoma and a visceral tumour). Approximately 20% of VHL disease diagnoses result from *a de novo* mutation and do not have a family history (Evans et al. Am J Med Genet A. 2010;152A:327-32). A molecular diagnosis of VHL indicates a risk of developing clinical VHL, but in the absence of tumour formation does not constitute a clinical diagnosis.

8.25. The Committee noted a study conducted in the UK reported a prevalence of VHL syndrome of 1 in 91,111 people, with a birth incidence of 1 in 42,987 and a 21% de novo (or spontaneous) mutation rate (Evans et al. 2010). A study in Denmark reported estimates of vHL prevalence in 1 in 46 900 individuals and birth incidence of 1 in 27 300 live births (Binderup et al. Eur J Hum Genet. 2017;25:301-7).

8.26. The Committee considered the supplier-provided estimate of prevalence of 1 in 52,000 to be reasonable. The Committee considered that this number was reasonable based on international data, and a lack of New Zealand specific data.

8.27. The Committee noted the life expectancy for those with VHL has been reported to be 52.5 years (Wilding et al. J Med Genet. 2012;49:264-9).

8.28. The Committee noted data from Australian Institute of Health and Welfare (AIHW) 2023 and considered the mean age of people developing VHL-associated tumours is lower than the general population. The Committee noted the mean age for developing tumours associated with VHL was reported as: 25 years of age for retinal angiomas, 30 years for cerebellar haemangioblastomas, 40 years for renal cell carcinoma and 35 years of age for pancreatic neuroendocrine tumours.

8.29. The Committee noted that almost 50% of VHL mutation carriers and a third of non-carriers reported clinically relevant levels of disease-related distress, with a significant subset of partners (36%) of individuals reported moderate to high levels of VHL-related distress (Lammens et al, Clin Genet 2010;77 483-91).

8.30. The Committee noted individuals with VHL undergo active surveillance from diagnosis and New Zealand clinicians would likely follow the eviQ VHL risk management guidelines. The Committee considered this period of active surveillance prior to developing VHL associated clinical features is likely to be longer for those with familial VHL (due to predictive testing), but likely shorter for non-familial cases (due to diagnosis requiring clinical features).

8.31. The Committee considered the health need of individuals with VHL to be significant, as VHL culminates in severe conditions so requires frequent and intense surveillance. In addition, the Committee considered multiple tumours and subsequent surgeries could result in loss of organ function and require significant time away from whānau and work.

8.32. The Committee noted Kasparian et al. Eur J Hum Genet. 2015;23:34-40 that reported the results of a study of individuals with VHL and their carers in Australia. The study reported six individuals (46%) reported anxiety, and two reported (15%) depressive symptoms, warranting clinical assessment. In addition, it reported participants experienced difficulties coping with the consequences of VHL, with reminders of the disease ever-present in their lives. Several carers in the study reported ongoing uncertainty, anxiety, and frustration in relation to their family member's health, as well as the limitations imposed on their lifestyle as a consequence of their caregiver role.

8.33. The Committee considered that as VHL is a familial condition, whānau may have multiple members impacted by the disease. The Committee considered that therefore whānau may have to care for multiple members, and this may have a socioeconomic impact on the family.

Health benefit

8.34. The Committee noted the following publications or conference abstracts that reported results from the LS004 phase 2, open-label, single-group study in people with RCC-associated with VHL disease:

- Jonasch et al. Interim analysis 1, not published.
- Jonasch et al. N Engl J Med. 2021;385:2036-46
- Jonasch et al. J Clin Oncol. 2022;40 (suppl 16; abstr 4546)
- Srinivasan et al. Annals of Oncol. 2022;33 (suppl 7):S808-69

8.35. The Committee noted the Srinivasan et al. 2022; abstract reported data at a median follow up of 37.8 months (mo). The abstract reported the following:

- Of 61 individuals with RCC, objective response rate (ORR) was 64% (95% confidence intervals [CI] 50.6-75; 4 complete responses [CRs], 35 partial

responses [PRs]). Median time to response (TTR) was 11.1 mo (range, 2.7-30.5 mo), and median duration of response (DOR) was not reached (range, 5.4+ to 35.8+ mo).

- Of 22 with pancreatic neuroendocrine tumours (pNET), ORR was 91% (95% CI 70.8-98.9; 7 CRs, 13 PRs); median DOR was not reached (range, 11.0+ to 37.3+ mo).
- Of 50 people with central nervous system hemangioblastomas ORR was 44% (95% CI 30.0-58.7; 4 CRs, 18 PRs); median DOR was not reached (range, 3.7+ to 38.7+ mo). Of 16 evaluable eyes in 12 people with retinal hemangioblastomas, 100% showed improvement.
- 38 of 61 (62%) remained on treatment; primary reasons for treatment discontinuation were individual decision (n=11; 18%) and disease progression (n=6; 10%).
- Grade 3 treatment-related AEs (TRAEs) occurred in 18% (n=11); anaemia was most common (n=7; 11%). No grade 4 or 5 TRAEs occurred.

8.35.1. The Committee considered there was a lack of information presented in the abstract on the reasons people discontinued the study.

8.35.2. The Committee noted that median DOR was not reached and considered the data immature. The Committee noted that there was an increase in the number of people progressing at 42 months and considered the durability of response after 3 years is uncertain.

8.35.3. The Committee noted there were a small number of people with RCC tumours who experienced a complete response.

8.35.4. The Committee noted there was a higher ORR in people with pNETs, however noted this was a secondary endpoint of the trial.

8.35.5. The Committee noted that metastases, and RCC tumours with a need for surgery, were exclusion criteria in the trial.

8.35.6. The Committee noted unpublished data provided by the Supplier that reported people in the study had a high number of prior surgeries. The Committee noted there were a reduced number of surgeries post treatment with belzutifan.

8.35.7. The Committee noted that anaemia was a common side effect experienced by people treated with belzutifan. The Committee noted Jonasch et al. 2021 reported four people (7%) received blood transfusions owing to anaemia; with one person receiving three blood transfusions. A total of 12 individuals (20%) received erythropoietin-stimulating agents, with a median of 2.5 administrations (range, 1 to 17); 3 of the 12 received both an erythropoietin-stimulating agent and a blood transfusion.

8.35.8. The Committee noted the supplier had provided summary information on a non-treatment natural history-derived control group cohort (named the “VHL-Natural History Study (VHL-NHS)”. The Committee did not consider the VHL-NHS derived unmatched “control group” a direct comparator, and considered the VHL-NHS group was more severely affected than those in the phase II trial.

8.35.9. The Committee noted the LS004 study was small, including 61 people. The Committee considered the limited study size and unmatched controls having worse baseline prognoses, in effect a cohort study indirectly comparing quite

different subpopulations, limited the ability to interpret magnitude of health benefit.

8.35.10. The Committee considered the data was not mature, with medium DOR not reached in any tumour type.

8.36. Overall, the Committee considered the evidence shows evidence of strong health benefit, but the study was of low quality. The Committee considered this was due to the population size which is limited due to it being a rare disease.

8.37. The Committee noted the following studies:

- Choueriri et al. Nat Med. 2021;27:802-5.
- Dhawan et al. CNS Oncol. 2022;11:CNS91
- Zamarud et al. J Neurooncol. 2023;165:373-9.
- Thalji et al. Cureus. 2024;16:e52979.
- Neth et al. J Neurooncol. 2023;164:239-47
- Grimes et al. Retin Cases Brief Rep. 2022 16.
- Ercanbrack et al. Am J Ophthalmol Case Rep. 2024:33:102011.
- Cotton et al Retin Cases Brief Rep. 2023
- Jones et al. Retin Cases Brief Rep. 2023.
- Mustafi et al. Retina. 2023
- Else et al. Clin Cancer Res. 2024
- Pelle et al. J Natl Compr Canc Netw. 2022;20:1285-87

8.38. A clinician in Texas with 20 years of experience of treating individuals with VHL shared their experience with the Rare Disorders Advisory Committee and Pharmac staff. The Committee and Pharmac staff valued this opportunity and considered that a different perspective helped to frame the Committee's discussions.

8.39. The clinician noted that the advantages of the current surgical interventions for associated tumours are that they are certain to be able to control tumour growth.

8.40. The clinician noted that the disadvantages of the surgical treatment option is that there is a limited number of surgical excisions that can be performed, and that there is an aggregated burden from chronic pain. The clinician also noted that this results in people having time away from work and highlighted that the anxiety associated with the possibility of having further procedures cannot be overstated.

8.41. The clinician shared their experience of prescribing belzutifan, being fairly well tolerated and shrinking most lesions. They also noted they have observed reduction in hemangioblastomas, and pancreatic cysts, and some improvement in retinal cysts.

8.42. They shared they had observed decreased numbers of interventions associated with the administration of belzutifan, as well as a delayed need for them. They described a decrease in the burden of disease for individuals they were caring for.

8.43. The clinician described the difference in treatment pathway for individuals who were prescribed belzutifan. They noted that for people with prior procedures who have lesions that are potentially threatening, initiation of belzutifan treatment leads to tumour shrinkage as well as delaying the need for further interventions. They highlighted there was still a need for sequential imaging surveillance post-treatment to ascertain whether belzutifan was providing a sustained effect.

Suitability

8.44. The Committee noted belzutifan is administered as a daily oral tablet, this would be an increase in pill burden compared to the standard surveillance treatment.

8.45. The Committee considered that the delays to surgical treatment would provide a suitability benefit, reducing time away from paid work, their whānau and communities that is incurred during surgical procedures and their recovery time.

8.46. The Committee noted lived experience evidence that there was a lack of continuity of care in New Zealand, with individual surgeons and specialists using different treatment guidelines, and a lack of coordination between specialists. The Committee considered the use of belzutifan may provide some continuity of treatment and may improve outcomes for Maori, Pacific peoples and others who may be underserved by the health system through consistent use of the treatment rather than different surgical interventions mediated by multiple clinical specialities which might vary.

Cost and savings

8.47. The Committee considered the evidence suggests belzutifan treatment would delay further systemic or surgical treatment rather than resolve the tumours. The Committee considered magnitude of the delay time is uncertain, noting that median DOR was not reached in the clinical trial for any tumour-type. The Committee considered the use of belzutifan may reduce organ function loss associated with surgery or tumour growth.

8.48. The Committee considered there was a large variation in tumours, including volume, location and impact on organ function. The Committee considered individuals would have many tumours developing over a life span.

8.49. The Committee considered the amount of active surveillance scans would be similar if belzutifan were funded, however if imaging suggested disease was stable, it may reduce the need to visit a specialist to discuss the results.

8.50. The Committee noted the eviQ guidelines for active surveillance of the different tumour types observed in VHL disease. In renal cell carcinoma and pancreatic neuroendocrine tumours, this consists of an MRI every 2 years (EviQ, ID 397 v.10, VHL disease -risk management).

8.51. The Committee considered whether it was appropriate to discontinue belzutifan therapy when surgery is planned. The committee considered that most individuals with VHL have multiple tumours and would likely continue treatment with belzutifan.

8.52. The Committee noted concerns around the VHL-NHS as a control population and its applicability to the New Zealand context. This is based on its inclusion of a narrower and more highly surveilled cohort, than is in the proposed indication. However, considering the limited evidence in this area, the Committee considered it could be used to represent the comparator for economic modelling.

8.53. The Committee noted anaemia was a common side effect in the trial and would require monitoring, and treatment to effect erythropoietin production.

Funding criteria

8.54. The Committee considered it would be unlikely that treatment would be discontinued, as individuals may have multiple tumours and would require belzutifan to control tumour growth even with surgery.

8.55. The Committee considered Special Authority Criteria should reflect the trial criteria of a maximum RCC tumour size ≥3 cm.

Summary for assessment

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

Population	People with VHL diagnosis, requiring treatment for either non-metastatic renal cell carcinoma with lesions ≥3 cm, central nervous system hemangioblastomas, or non-metastatic primitive neuroectodermal tumour not requiring immediate surgery, with an ECOG 0-1, and no prior systemic anti-cancer therapy.
Intervention	120 mg belzutifan, once daily (3 x 40-mg tablets) until clinical progression or intolerable toxicity. Belzutifan can be continued upon/despite radiographic progression if the individual is not experiencing clinical progression and the treating clinician assesses the patient is still deriving clinical benefit.
Comparator(s)	Active surveillance based on the eviQ guidelines for VHL disease risk management (EviQ, ID 397 v.10, VHL disease -risk management).
Outcome(s)	The main benefit associated with belzutifan compared to active surveillance is prolonging the time spent without the need for surgery. The LITESPARK-004 (intervention) and VHL Natural History study (comparator) publications provide evidence of this benefit and inform transition probabilities for economic modelling. Potential model health states are outlined below: • Pre-surgery (all participants start in this health state) • Surgery • Event free after surgery • Metastatic disease • Dead The avoidance of surgery is important to clinicians, people experiencing VHL-associated tumours, and health systems/ waiting times for surgery for other conditions.
Table definitions: Population, the target population for the pharmaceutical; Intervention, details of the intervention pharmaceutical; Comparator, details the therapy(s) that the target population would receive currently (status quo – including best supportive care); Outcomes, details the key therapeutic outcome(s) and source of outcome data.	

9. Agalsidase beta for Fabry disease

Application

9.1. The Committee noted that Pharmac staff sought updated advice from the Committee regarding agalsidase beta for the treatment of Fabry disease, in light of a new submission from Sanofi-Aventis New Zealand Limited.

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

Recommendation

9.3. The Committee **recommended** that agalsidsase beta for Fabry disease be listed with a **high priority** within the context of treatments for rare disorders, subject to the following Special Authority criteria (content the same as that recommended previously for agalsidase alfa):

> **Special Authority for Subsidy**
> **Initial application** – from any relevant practitioner. Approvals valid for 12 months for

applications meeting the following criteria:
Both:

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

Renewal –from any relevant practitioner specialist. Approvals valid for 12 months for applications meeting the following criterion:

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

9.4. In making this recommendation, the Committee noted that:

- PTAC had previously considered in May 2006 and November 2011 (in particular) that there was limited evidence for clinical benefit, including a lack of translation into improved organ function or delayed clinical progression in patients with Fabry disease, from agalsidase beta.

- The Rare Disorders Advisory Committee (previously Subcommittee) had recommended a similar enzyme replacement therapy, agalsidase alfa, for Fabry disease be listed with a medium priority in November 2018 and reaffirmed this recommendation in March 2023. The recommendation was based on health need, a lack of alternative treatment options, and low to-moderate level of evidence including observational evidence of real-world benefit.

- In 2018, the Rare Disorders Subcommittee had considered the evidence supports that agalsidase alfa and beta provide similar benefits and commercial competition between products could provide an opportunity to manage costs and improve the cost effectiveness of treatments for Fabry disease.

9.4.1. Considered that, based on its current review:

- The evidence for both agalsidase alfa and agalsidase beta for Fabry disease had continued to develop since it was reviewed by the Committee in 2018 and 2023.
- The evidence continues to indicate that the health benefits from agalsidase alfa and agalsidase beta are similar and these two medicines could be considered interchangeable for the treatment of Fabry disease.
- The high health need of people with Fabry disease was a significant factor in giving agalsidase beta a high priority recommendation.

- That the medium priority recommendation currently in place for agalsidase alfa would similarly be considered a high priority at this time for the same reasons.

Discussion

Māori impact

9.5. The Committee discussed the impact of funding agalsidase beta for the treatment of Fabry disease on Pharmac's Hauroa Arotahi: Māori health areas of focus and Māori health outcomes. The Committee noted that there are few known Māori families with Fabry disease and considered that Māori were not overrepresented in this disease.

Impact on Pacific peoples, disabled people, tāngata whaikaha Māori, and other people who have been underserved by the health system

9.6. The Committee discussed the impact of funding agalsidase beta for the treatment of Fabry disease on Pacific peoples, disabled people, tāngata whaikaha Māori, and other people who have been underserved by the health system.

Background

9.7. The Committee noted that Pharmac staff sought advice on agalsidase beta in light of an updated submission from the supplier. The Committee noted it, or PTAC, had previously considered agalsidase alfa, agalsidase beta and migalastat many times, with the most recent discussion regarding treatments for Fabry disease occurring in March 2023. The Committee noted the current status of these applications as follows:

- agalsidase alfa - ranked to the Options For Investment list.
- agalsidase beta – seeking clinical advice.
- migalastat - under assessment.

Health need

9.8. The Committee noted that a family living with Fabry disease had shared their experience with it and Pharmac staff at the Committee's March 2023 meeting.

9.9. The Committee noted the biological and genetic basis of Fabry disease, a multi-organ x-linked inborn error of metabolism, which has also been detailed in previous meeting records. The Committee noted that cardiac, renal and cerebrovascular disease are the major causes of morbidity and mortality in Fabry disease. The Committee noted that Fabry disease symptoms arise from lysosomal accumulation of glycolipid substrate enzymes, which leads to end-organ disease. The Committee noted that health-related quality of life limitations in people with Fabry disease are challenging to quantify but considered that these are substantial. The Committee considered that while some individuals are carriers with dormant disease who do not experience effects from the disease, others are severely affected by Fabry disease and this impact would increase with age.

9.10. The Committee considered that the population described by the Special Authority criteria previously recommended for agalsidase alfa would also accurately define the population suitable for treatment with agalsidase beta. The Committee noted that in New Zealand, females are overrepresented in this disease mostly due to diagnosis after paternal death, with cardiac issues historically driving diagnosis rates.

9.11. The Committee noted that only a few new diagnoses of Fabry disease had occurred in the past year in New Zealand and there had been no new deaths reported. The Committee considered that Pharmac staff could obtain current registry data for the

number of people in New Zealand with Fabry disease, including the number with *GLA* mutational variants responsive to migalastat, from the Adult and Paediatric National Metabolic Service clinical database to create greater precision in its analysis of this proposal. However, the Committee considered the following issues present challenges for defining the size of the New Zealand population with Fabry disease whose disease may be clinically appropriate for treatment:

9.11.1. Current screening panels may not be effectively identifying people with Fabry disease that has a Taiwanese mutational variant known to be associated with cardiomyopathy.

9.11.2. There are likely to be a proportion of unidentified and undiagnosed people with Fabry disease (eg among those on kidney dialysis or people who have experienced a stroke).

9.11.3. It is challenging to identify which people with Fabry disease are at risk of symptomatic disease progression and in which organ system(s).

9.12. The Committee considered that the health needs of those with Fabry disease in New Zealand has not changed since last considered by the Committee in 2023 and that the ongoing unmet need is in those with symptomatic Fabry disease has increased associated with this time delay.

9.13. The Committee noted there remains no Fabry disease-specific treatment funded in New Zealand. The Committee noted that a small number of New Zealand people with Fabry disease are currently receiving gene therapy through a clinical trial in Australia, and small number are receiving post-clinical trial compassionate access treatment with migalastat.

Health benefit

9.14. The Committee noted that agalsidase beta is an enzyme replacement therapy (ERT) that is administered as an intravenous (IV) infusion at a recommended dose of 1 mg/kg per dose every two weeks. The Committee noted that Medsafe approval for agalsidase beta has lapsed.

9.15. The Committee noted that the there was a global shortage of agalsidase beta in 2010, which led to many individuals in other countries who were receiving agalsidase beta switching to agalsidase alfa, and that this was apparent in the evidence base. The Committee noted that internationally, agalsidase beta is used for a greater proportion of those with Fabry disease compared with agalsidase alfa, although considered it was not an evidence-based preference.

9.16. The Committee noted the following publications:

- Ramaswami et al. Mol Genet Metab. 2019;127:86-94 (including Supplementary tables, supplementary figures and supplementary material). The Committee noted the authors reported there was no consistent benefit from low-dose regimens of agalsidase beta.
- Goker-Alpan et al. JIMD Rep. 2016:25:95-106
- Sirrs et al. Mol Genet Metab. 2014;111:499-506
- El Dib et al. Cochrane Database Syst Rev. 2016;7:CD006663
- El Dib et al. PLoS One. 2017;12:e0173358
- Oritz et al. J Med Genet. 2016;53:495-502
- Kramer et al. Nephrol Dial Transplant. 2018;33:1362-72
- Arends et al J Med Genet 2018; 55(5):351-8

- Lenders et al. J Med Genet. 2021;58:342-50

9.17. The Committee considered that the new evidence was primarily from three small observational studies and that the overall evidence base for agalsidase beta for Fabry disease is of relatively poor strength and quality, as expected for clinical evidence in the treatment of a rare disorder. The Committee considered that the new evidence did not change the Committee's previous assessment of the health benefits of agalsidase beta.

9.18. The Committee noted that the evidence has continued to develop for both agalsidase beta and agalsidase alfa and that it reports similar incidence of key clinical outcomes such as stroke, cardiac events and renal deterioration with each treatment. The Committee noted that there remained no clear evidence for superiority of either agalsidase alfa or agalsidase beta, and that the available studies indicate the two ERTs provide very similar health benefits in Fabry disease, and thus the Committee considered the two interchangeable in terms of health benefit.

9.19. The Committee considered that the larger proportion of agalsidase beta use compared with agalsidase alfa globally has resulted in greater familiarity. However, the Committee considered the two treatments would similarly address the current unmet health need in New Zealand.

9.20. The Committee considered that people with non-migalastat responsive Fabry disease who have early end organ disease would be the subgroup anticipated to receive the greatest benefit from treatment with agalsidase beta, as with agalsidase alpha. The Committee noted that the data did not provide clear, appropriate, high-quality evidence for use in economic modelling, however, considered that the specific health benefits expected from treatment with agalsidase beta (or indeed alpha) for Fabry disease are as follows:

9.20.1. Slower decline in renal function (annualised mean change in eGFR)

9.20.2. Slower progression of cardiac disease (mean rate of left ventricular mass index [LVMI] increase)

9.20.3. A reduced risk of stroke

9.20.4. Longer survival

9.20.5. Improved health-related quality of life, including pain-related quality of life.

9.21. The Committee considered that the family and whānau of people with Fabry disease would receive a benefit (ie financial, physical and/or mental well-being) from an individual with Fabry disease receiving direct health benefits from treatment with agalsidase beta, agalsidase alfa or migalastat that result in the individual living longer, being less disabled, spending less time on dialysis and/or being able to work longer.

Suitability

9.22. The Committee noted that agalsidase beta requires a comparatively long intravenous (IV) infusion of about five hours for the initial dose, reducing to a minimum of two hours in those who have no associated infusion reactions (as opposed to agalsidase alfa which is infused over a period of 40 minutes). The Committee considered that this would be manageable for individuals and healthcare providers, however it would be a significant change for people living with Fabry disease who currently receive no active treatment for the disease.

Cost and savings

9.23. The Committee considered that prompt treatment would be appropriate for people with Fabry disease-related symptom(s), rather than upon them developing multiple complications from symptomatic disease. The Committee considered that the Special Authority criteria could identify a broad group of people with Fabry disease, although considered that clinicians may consider treatment unlikely to be beneficial for those with end-stage organ disease, and clinicians may consider also that those who are completely asymptomatic and at low risk of progression may not require treatment. The Committee was informed that, of the group who would be targeted by the funding criteria, there were approximately 15 people who would be initiated on treatment if ERT were funded and 11 of those people would receive migalastat instead, if it were funded.

9.24. The Committee was informed that the size of the total treatable pool of people with Fabry disease in New Zealand is unlikely to change significantly over time, as only a small proportion of people with Fabry disease on surveillance would develop disease symptoms requiring treatment (eg females with cardiomyopathy developing at an older age). The Committee considered that the number of people with Fabry disease eligible for treatment would be expected to increase by approximately one per year, on average, based on two new diagnoses per year, and that this group includes roughly similar proportions of males and females.

9.25. The Committee considered that, if migalastat and either agalsidase alfa or agalsidase beta were funded:

9.25.1. A greater proportion of people with Fabry disease in New Zealand would be expected to be eligible for migalastat compared with overseas (approximately 75%, compared to 30-50% internationally), due to the higher proportion of those with cardiac variants known to be responsive to migalastat in New Zealand. It is not known why this is the case, however it may be influenced by:

- the inherited nature of the disease and the small total number of people with the condition in New Zealand
- higher rates of diagnosis based on testing for a known cardiac variant in people with cardiac disease, due to the high uptake of gene panels in this population.

9.25.2. People with Fabry disease who have a *GLA* mutational variant that is responsive to migalastat would receive that treatment initially, noting the additional suitability benefit of its oral formulation. This would be approximately one in six of all people with Fabry disease in New Zealand, and 11 of the approximately 15 people who would initiate ERT treatment.

9.25.3. If migalastat were to be funded, agalsidase alfa or agalsidase beta would also need to be funded for the remaining people with Fabry disease who would benefit from treatment but do not have migalastat-amenable mutational variants (approximately 4 of 15 people).

9.25.4. Uptake of (any) treatment for Fabry disease would likely be 100% in the proportion of people with Fabry disease who would benefit from treatment.

9.25.5. Migalastat would not be used in combination with agalsidase alfa or agalsidase beta, noting it is targeted to a subgroup with Fabry disease with responsive mutations and would be preferred as a first-line treatment.

9.26. The Committee considered it is unclear whether the rate of diagnosis of Fabry disease would increase if treatment(s) for Fabry disease were funded. The Committee considered that Fabry disease is a rare disorder that can be difficult to

identify without specialist knowledge, testing for Fabry disease is not a candidate for newborn screening, and it is unclear in which organ system an individual will progress (eg those with undiagnosed Fabry disease who have cardiac or renal problems which may or may not progress depending on risk features).

9.27. The Committee considered that additional costs would be associated with agalsidase beta (or alpha) due to IV infusions, compounding and monitoring (eg cardiac monitoring). The Committee considered that health sector savings may occur as a result of reductions in renal dialysis and cardiac procedures.

Funding criteria

9.28. The Committee considered that the Special Authority criteria previously recommended for agalsidase alfa in March 2023 were also appropriate to be applied to agalsidase beta, noting that these identify individuals with Fabry disease-related clinical problems that are substantial enough to require treatment. The Committee considered that the criteria were appropriate to enable clinician judgement of treatment suitability and potential benefits whilst effectively targeting the group who would benefit most.

9.29. The Committee specifically considered the renal criteria within the Special Authority and confirmed the definition of impairment (with a minor correction to differentiate proteinuria from urinary albumin:creatinine ratios) was appropriate and evidence based as a marker of renal disease in Fabry disease, despite being set at what would be considered relatively low thresholds for renal impairment generally in other clinical contexts.

9.30. The Committee considered that if there was any further consideration or advice on Fabry treatments sought in future, then that advice should include the role and priority of migalastat, and be provided on all the three treatments (agalsidase alfa, agalsidase beta, migalastat) considered together.

Summary for assessment

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

Population	People with Fabry disease, including those whose disease is not responsive to migalastat, who have at least one of the following complications: • Renal disease • Cardiac disease • Ischaemic vascular disease • Uncontrolled chronic pain • Fabry-related gastrointestinal issues • Other manifestation with significant HRQoL impacts as determined by relevant specialist
Intervention	Agalsidase beta 1mg/kg every other week via 15mg/hour intravenous infusion. Treatment can continue long-term if the individual is still benefitting.
Comparator(s)	Best supportive care and treatment of symptoms.

Outcome(s)	• Slower decline in renal function • Slowed progression of cardiac disease • Reduced risk of stroke • Longer survival • Improved HRQoL, including pain-related quality of life Magnitude of benefit comparable to both agalsidase alfa and migalastat
Table definitions: Population, the target population for the pharmaceutical; Intervention, details of the intervention pharmaceutical; Comparator, details the therapy(s) that the target population would receive currently (status quo – including best supportive care); Outcomes, details the key therapeutic outcome(s) and source of outcome data.	

10. Avalglucosidase alfa for Pompe disease, infantile onset (IOPD)

Application

10.1. The Advisory Committee reviewed the application avalglucosidase alfa for the treatment of infantile onset Pompe disease.

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

Recommendation

10.3. The Advisory Committee **recommended** that avalglucosidase alfa for the treatment of infantile onset Pompe disease be funded with a **medium priority** within the context of treatments for rare disorders subject to the following Special Authority criteria:

> **Initiation** (Pompe disease). Applications prescribed by or recommended by a metabolic physician. Approvals valid for 12 months for applications meeting the following criteria:
> All of the following:
> 1. The patient is aged up to 24 months at the time of initial application and has been diagnosed with Pompe disease; and
> 2. Any of the following:
> 2.1. Diagnosis confirmed by documented deficiency of acid alpha-glucosidase by prenatal diagnosis using chorionic villus biopsies and/or cultured amniotic cells; or
> 2.2. Documented deficiency of acid alpha-glucosidase, and documented molecular genetic testing indicating two disease-causing mutational variants in the acid alpha-glucosidase gene (GAA gene); or
> 2.3. Documented urinary tetrasaccharide testing indicating a diagnostic elevation of glucose tetrasaccharides, , and documented molecular genetic testing indicating two disease-causing mutational variants in the *GAA* gene ; and
> 3. The patient has not required long-term invasive ventilation for respiratory failure prior to starting enzyme replacement therapy (ERT); and
> 4. The patient does not have another life-threatening or severe disease where the prognosis is unlikely to be influenced by ERT or might be reasonably expected to compromise a response to ERT.
>
> **Continuation** (Pompe disease). Applications prescribed by or recommended by a metabolic physician. Approvals valid for 12 months for applications meeting the following criteria:
> All of the following:
> 1. The treatment remains appropriate for the patient and the patient is benefiting 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 ERT; and
> 3. Patient has not developed another medical condition that might reasonably be expected to compromise a response to ERT; and
> 4. There is no evidence of life-threatening progression of respiratory disease as evidenced by the needed for >14 days of invasive ventilation; and
> 5. There is no evidence of new or progressive cardiomyopathy.

10.4. In making this recommendation the Committee considered:

- The high health need of children with infantile onset Pompe disease
- Avalglucosidase alfa is likely non-inferior to currently funded alglucosidase alfa
- The lack of evidence of health benefit in children aged less than 1 years old. The Committee noted this evidence would not be available until 2026.
- The ability to increase dosing to 40mg/kg to improve efficacy, which is not currently available based on the Special Authority criteria for alglucosidase alfa

10.5. The Committee considered the funding of avalglucosidase alfa would be a high priority if alglucosidase alfa is discontinued worldwide.

Discussion

Māori impact

10.6. The Committee discussed the impact of funding avalglucosidase alfa for the treatment of infantile onset Pompe disease (IOPD) on Pharmac's Hauroa Arotahi: Māori health areas of focus and Māori health outcomes.

10.7. The Committee noted a study investigating the barriers and considerations for diagnosing rare diseases in indigenous populations. The study reported that significant barriers remain regarding access to diagnosis for Indigenous populations, including but not limited to poorer access to genomic technologies and the research that drives them, which prevent Indigenous peoples from receiving appropriate benefits from genomic and other new knowledge (D'Angelo et al. Front Pediatr. 2020:8:579924).

Impact on Pacific peoples, disabled people, tāngata whaikaha Māori, and other people who have been underserved by the health system

10.8. The Committee considered Pacific peoples and other people who have been underserved by the health system experience similar barriers to accessing healthcare as Māori.

Background

10.9. The Committee noted alglucosidase alfa for the treatment of IOPD had been reviewed by both the then Rare Disorders Subcommittee (in November 2014) and PTAC (in 2009 and 2011). The 2014 considerations specific to IOPD included:

- *"The Subcommittee noted that treatment of the infantile form with ERT [enzyme replacement therapy] had been shown to prolong life and reduce the need for mechanical ventilation.*
- *The Subcommittee considered this medication could be life-saving for young children with the infantile form. The Subcommittee also noted that the improved quality of life from the new treatment in infants would mean that they would be alive and ventilator free, if commenced early enough.*
- *The Subcommittee noted that the patient population to benefit most from this treatment would be infants. The Subcommittee noted that no applications for patients with infantile Pompe had been submitted through the NPPA process. The Subcommittee considered that alglucosidase alfa could be funded for patients with infantile Pompe disease if agreement with the supplier could be reached."*

10.10. Alglucosidase alfa has been listed on the Pharmaceutical Schedule under Special Authority for the treatment of IOPD since December 2016.

Health need

10.11. The Committee noted it had considered the health need of people with late onset Pompe disease in November 2018, and the earlier PTAC and Subcommittee considerations of IOPD in 2009 to 2014.

10.12. The Committee noted the most severe form of Pompe disease, infantile onset Pompe disease (IOPD), is present at birth or presents in the first year of life and is characterised by cardiomyopathy, severe muscle hypotonia and respiratory insufficiency; whereas late onset Pompe disease (LOPD) may begin from 1 year of age through late adulthood with development of progressive motor disability and respiratory insufficiency (Toscano et al Ann Transl Med. 2019;7:284).

10.13. The Committee noted individuals with IOPD have a severe or complete acid alpha glucosidase (GAA) deficiency with less than 1% of GAA activity (Kishnani et al. J Pediatr. 2006;148:671-76).

10.14. The Committee noted there are reportedly no individuals currently alive with IOPD in New Zealand. The global incidence of IOPD is commonly reported to be 1 in 150,000 births. Clinical studies elucidate that 28% of Pompe disease cases are IOPD cases (Al-Hassnan et al. Orphanet J Rare Dis. 2022;17:388).

10.15. The Committee noted the health need for IOPD is severe as the condition is rapidly progressive, and the majority of untreated individuals die within the first year of life. The disease course is characterised by hypertrophic cardiomyopathy and muscle weakness, and death is due to a combination of ventilatory and cardiac failure. Infants/children do not experience any motor developmental milestones such as turning, sitting, or standing. The median age of death in individuals with untreated IOPD had previously been reported to be 8.7 months (Kishnani et al. 2006), with a range between approximately 5-9 months, and survival beyond the age of 18 months is exceptional (Hahn. et al. Ann Transl Med. 2019; 7: 283).

10.15.1. The Committee noted Kishnani et al. 2006 reported the median age at symptom onset was 2.0 months (range 0 to 12 months), 4.7 months at diagnosis (range: prenatal to 84.2 months), 5.9 months at first ventilator support (range 0.1 to 39.5 months), and 8.7 months at death (range 0.3 to 73.4 months). Survival rates at 12 months of age were 25.7% overall and 16.9% ventilator-free: at 18 months 14.3% and 8.5%. Cardiomegaly (92%), hypotonia (88%), cardiomyopathy (88%), respiratory distress (78%), muscle weakness (63%), feeding difficulties (57%), and failure to thrive (53%) appeared after a median age of approximately 4.0 months.

10.15.2. The Committee noted a study of 20 cases of IOPD reported in Dutch centres and 133 found in literature, reported symptoms starting at a median age of 1.6 months in both groups, the median age of death being 7.7 and 6 months, respectively. Five percent of the Dutch individuals and 8% of all reported individuals survived beyond 1 year of age. Only 2 individuals from literature survived more than 18 months (Van den Hout et al.Pediatrics. 2003;112:332-40).

10.16. The Committee noted respiratory distress and feeding difficulties are commonly observed in IOPD, and infants can require continuous and/or invasive supports, such as ventilation, nasogastric tubes, or percutaneous endoscopic gastrostomy. In addition IOPD significantly affects children's quality of life (QoL), including physical, emotional, and social functioning related to their health state (Benedetto et al. Behav Sci (Basel). 2023;13:956).

10.17. The Committee noted a 2023 study of parents caring for a child with treated IOPD that reported a total of 57.1% of parents lived with moderate/severe burden

conditions; worse QOL for the child was associated with higher levels of caregiver burden (r_S[N = 14] = −0.67, p < 0.01). Uncertainty about the child's future was a state commonly described by mothers (Benedetto et al. 2023).

10.18. The Committee noted a 2013 study (Kanters et al. Mol. Genet. Metab. 2013;110:281-6) that reported higher levels of burden and worse health outcomes among primary caregivers, typically parents (94%), of children with IOPD compared to caregivers of adults. In prioritising the child's needs, parents also face difficulties in balancing family life (including marital and sibling relationships) and fulfilling work obligations, with an increase in stress and conflicts (Benedetto et al. 2023).

10.19. The Committee noted that alglucosidase alfa, funded for IOPD since 2016, will be discontinued globally, although a timeline for this has not been provided.

10.20. The Committee noted that no individuals with IOPD in New Zealand have received funded alglucosidase alfa since funding inception 8 years ago.

10.21. The Committee considered one to two individuals might have been born with IOPD since 2016, based on incidence data internationally. The Committee considered the apparent lack of individuals identified, compared with expected, indicated a potential issue with access to treatment or diagnosis. The Committee considered that due to the lack of newborn screening, and the challenging diagnosis, some infants would not be diagnosed with IOPD, however it is likely they would have been diagnosed post mortem on genetic testing.

10.22. The Committee considered some individuals present later in early childhood with neuromuscular disease, but they may not be diagnosed due to a disconnect between different clinical services so that testing for Pompe disease may not be performed.

Health benefit

10.23. The Committee noted Kishnani et al. Genet Med. 2023;25:100328 reported the results of the Mini COMET phase 2, open-label, ascending-dose, 3-cohort study of avalglucosidase alfa in 22 individuals with IOPD aged <18 years who had previously received alglucosidase alfa and subsequently experienced clinical decline (cohorts 1 and 2) or suboptimal response (cohort 3) at 6 months:

- During the 25-week primary analysis period, cohorts 1 (n=6) and 2 (n=5) received avalglucosidase alfa 20 and 40 mg/kg every other week, respectively, for 6 months, cohort 3 (n=6) randomised (1:1) to receive avalglucosidase alfa 40 mg/kg every other week or alglucosidase alfa (current stable dose) for 6 months.
- A total of 5 individuals were receiving ventilation at baseline, and no new invasive ventilator use was reported during the trial.
- All participants' heart size remained within the normal range or improved.
- Among ambulatory individuals aged ≥6 years at baseline, 6MWT distance improved for all receiving 40 mg/kg of avalglucosidase alfa every other week in cohorts 2 and 3. Cohort 1 and the cohort 3 alglucosidase alfa recipients were stable or declined during the trial.
- Gross Motor Function Measure-88 (GMFM-88) improved across all cohorts despite heterogeneous baseline functional levels and greater severity in cohorts 1 and 2. GMFM-88 total percent score (mean) improved modestly in all cohorts, with high interindividual variability. Quick Motor Function Test (QMFT) total score improved in cohorts 2 and 3, whereas mean score in cohort 1 remained stable.
- Proportions of individuals with treatment-emergent adverse events were similar across dose and treatment groups. No serious or severe treatment-related

treatment-emergent adverse events occurred. None of the individuals discontinued treatment or died.

10.23.1. The Committee considered while the trial was of short duration, it reported substantial health benefit in a rapidly clinically declining population.

10.23.2. The Committee considered the higher dose appeared more efficacious, but the magnitude of benefit was uncertain due to the small trial population and lack of long-term data.

10.24. The Committee noted a single group, Phase 3, open label study to assess efficacy, safety, pharmacokinetic, pharmacodynamics of avalglucosidase alfa in treatment naïve babies with IOPD under 12 months of age (Baby COMET) is underway and planned to be completed in August 2026. The Committee noted avalglucosidase alfa has been submitted for Medsafe registration for the treatment of individuals one year of age and older with Pompe disease.

10.25. The Committee considered the benefit of ERT in IOPD (avalglucosidase alfa or alglucosidase alfa) was greatest when provided as soon as practicable after disease onset or diagnosis.

10.26. The Committee noted the following longitudinal follow-up extension or other studies that observed long-term clinical outcomes with alglucosidase alfa in IOPD:

- Kishnani et al. Neurology. 2007;68:99-109.
- Kishnani et al. Pediatr Res. 2009;66:329-35.
- Nicolino et al. Genet Med. 2009;11:210-9
- Hahn et al. Genet Med. 2018;20:1284-94
- Broomfield et al. J Inherit Metab Dis. 2016;39:261-71
- Parini et al. Orphanet J Rare Dis. 2018;13:32.
- Chien et al. J Pediatr. 2015;166:985-91.e1-2
- Nagura et al. Neurol Ther. 2019;8:397-409

10.27. The Committee noted the view of the supplier applicant that avalglucosidase alfa has similar efficacy and safety to currently-funded alglucosidase alfa in IOPD, based on the Kishnani 2023 Mini-COMET results.

10.27.1. The Committee noted a lack of comparative evidence between avalglucosidase alfa and alglucosidase alfa in IOPD but noted likely non-inferiority in the LOPD setting (as discussed by the Committee separately during the meeting) and considered there were no biologically plausible reasons why that feature would not translate to the IOPD setting. The Committee hence considered avalglucosidase alfa would likely be non-inferior to alglucosidase alfa in IOPD too.

Suitability

10.28. The Committee noted the infusion time for avalglucosidase alfa was the same as that of the currently funded alglucosidase alfa.

Cost and savings

10.29. The Committee noted 25% of people with IOPD have a cross-reactive immunologic material (CRIM)-negative status (Al-hassnan et al. 2022). The Committee considered most people receiving treatment for Pompe disease would first be treated with methotrexate or rituximab to dampen the immune response and therefore make less

antibodies against the treatment. This approach would be followed irrespective of which ERT treatment (avalglucosidase alfa or alglucosidase alfa) is administered.

10.30. The Committee considered there might be a reduction in pharmacy preparation time in comparison to alglucosidase alfa.

10.31. The Committee considered most people would receive the higher 40mg/kg dose if avalglucosidase alfa was funded for IOPD.

Funding criteria

10.32. The Committee considered individuals should be able to titrate up to a maximum dose of 40mg/kg body weight every two weeks if necessary to experience optimal clinical response.

Summary for assessment

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

Population	Infantile-onset Pompe disease
Intervention	Avalglucosidase alfa 20mg/kg IV every two weeks. If there is a lack of improvement or the individual experiences insufficient response in cardiac, respiratory, and/or motor function while on 20mg/kg dose, the dose can be increased to 40 mg/kg every two weeks. Individuals continue on treatment until they no longer experience clinical improvement or stabilisation associated with treatment.
Comparator(s)	Alglucosidase alfa 20mg/kg IV every two weeks. Individuals continue on treatment until they no longer experience clinical improvement or stabilisation associated with treatment. A dose increase is not currently funded. *Note that if alglucosidase alfa is discontinued worldwide, the comparator will be best supportive care as there will be no funded treatment options available.*
Outcome(s)	The supplier claims that avalglucosidase alfa demonstrates similar efficacy and safety to alglucosidase alfa, based on the findings from Mini-COMET, in which the following outcomes were assessed for children up to age two years: • Gross motor function and endurance (GMFM 88, QMFT, 6MWT) • Mobility function (Pompe PEDI mobility score) • Maintenance of cardiac function ((EchoLVM) • Maintenance of respiratory function (ventilator use) Based on this claim, the supplier assumes the survival benefit with alglucosidase alfa may be used as a proxy for avalglucosidase alfa. A pooled analysis provided by the supplier indicates that in IOPD, the risk of death is reduced by 91% for people treated with to alglucosidase alfa compared with natural history (HR 0.09; 95% CI: 0.06, 0.13).
Table definitions: Population, the target population for the pharmaceutical; Intervention, details of the intervention pharmaceutical;	

Comparator, details the therapy(s) that the target population would receive currently (status quo – including best supportive care);
Outcomes, details the key therapeutic outcome(s) and source of outcome data.

11. Avalglucosidase alfa for Pompe disease, late onset (LOPD)

Application

11.1. The Advisory Committee reviewed the application for avalglucosidase alfa for the treatment of late onset Pompe disease.

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

Recommendation

11.3. The Advisory Committee **recommended** that avalglucosidase alfa for the treatment of late onset Pompe disease be funded with a **medium priority**, within the context of treatments for rare disorders, subject to the following Special Authority criteria:

> **Initiation** (Pompe disease). Applications prescribed by or recommended by a metabolic physician. Approvals valid for 12 months for applications meeting the following criteria:
> All of the following:
> 1. Patient has been diagnosed with Pompe disease; and
> 2. Any of the following:
> 2.1. Diagnosis confirmed by documented deficiency of acid alpha-glucosidase by prenatal diagnosis using chorionic villus biopsies and/or cultured amniotic cells; or
> 2.2. Documented deficiency of acid alpha-glucosidase, and documented molecular genetic testing indicating two disease-causing mutational variants in the acid alpha-glucosidase gene (GAA genee; or
> 2.3. Documented urinary tetrasaccharide testing indicating a diagnostic elevation of glucose tetrasaccharides, and molecular genetic testing indicating a disease-causing mutational variant in the GAA gene; and
> 3. The patient has not required long-term invasive ventilation for respiratory failure prior to starting ERT; and
> 4. The patient does not have another life-threatening or severe disease where the prognosis is unlikely to be influenced by ERT or might be reasonably expected to compromise a response to ERT.
>
> **Continuation** (Pompe disease). Applications prescribed by or recommended by a metabolic physician. Approvals valid for 12 months for applications meeting the following criteria:
> All of the following:
> 1. The treatment remains appropriate for the patient and the patient is benefiting 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 ERT; and
> 3. Patient has not developed another medical condition that might reasonably be expected to compromise a response to ERT; and
> 4. There is no evidence of life-threatening progression of respiratory disease as evidenced by the needed for >14 days of invasive ventilation; and
> 5. There is no evidence of new or progressive cardiomyopathy.

11.4. In making this recommendation, the Committee considered:

- The high health need of people with late onset Pompe disease
- The lack of funded treatment options
- The health benefit evidence was of moderate to good strength and quality but was based on limited numbers of participants and limited follow up data.
- The health benefit evidence indicates avalglucosidase alfa treatment may not improve the individual's symptoms but should slow at least the decline in health.

- The trial endpoints were surrogate measures of clinical outcomes, but although it is uncertain how these measures would extrapolate to overall survival based on currently available data, the surrogate results nonetheless suggested improvements or arrested declines that were likely clinically meaningful.
- The additional burden on infusion services.

Discussion

Patient lived experience

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

11.6. The individual recounted their extended delay to diagnosis and the lack of funded medicines for their disease. They shared their challenging treatment journey including multiple clinical trials with extended periods away from their family and whānau for treatment. They expressed concerns over the inadequate access to treatment in New Zealand, with current access through international compassionate access funded by pharmaceutical suppliers.

11.7. They detailed the high burden on people with the disease to seek out treatment through compassionate access schemes, which relies on a high level of health literacy. They also described the mental strain this also placed on the individuals with the disease.

11.8. The individual shared their personal experience of accessing alglucosidase alfa treatment. They said for them the treatment reduced their symptom burden, as well as slowed the progress of their disease to allow them to live a full life including spending time with their grandchildren.

11.9. They shared how visits to the infusion clinic for treatment also provided a social aspect that they enjoy, and treatment has prevented the need to visit the respiratory specialists or metabolic team in person.

Māori impact

11.10. The Committee discussed the impact of funding avalglucosidase alfa for the treatment of late onset Pompe disease (LOPD) on Pharmac's Hauroa Arotahi: Māori health areas of focus and Māori health outcomes.

11.11. The Committee noted a study investigating the barriers and considerations for diagnosing rare diseases in indigenous populations. The study reported that significant barriers remain regarding access to diagnosis for Indigenous populations, including but not limited to poorer access to genomic technologies and the research that drives them, which prevent Indigenous peoples from receiving appropriate benefits from genomic and other new knowledge (D'Angelo et al. Front Pediatr. 2020:8:579924).

11.12. The Committee considered there was a lack of data to suggest if LOPD disproportionally affects Māori, however was informed Māori are overrepresented in the number of people with LOPD in New Zealand due to a large whānau being affected.

Impact on Pacific peoples, disabled people, tāngata whaikaha Māori, and other people who have been underserved by the health system

11.13. The Committee considered Pacific peoples experience similar barriers to accessing healthcare as Māori. The Committee considered there was a lack of data to suggest if LOPD disproportionally affects Pacific peoples.

11.14. The Committee considered as LOPD is an inherited disease, nationalities, ethnic groups and cultures with higher incidences of consanguinity (Bittles & Black. Proc Natl Acad Sci U S A. 2010;107(Suppl 1):1779-86) may have higher incidence of LOPD. The Committee considered this might affect individuals including some refugees and asylum seekers, who already have poorer access to health care from language and cultural barriers.

Background

11.15. The Committee noted alglucosidase alfa for the treatment of LOPD had been extensively reviewed by both the Committee and PTAC, the Committee most recently in 2018, where it had recommended the application for alglucosidase be declined.

11.15.1. The Committee had at the time also expressed interest a re-submission for alglucosidase alfa targeted to the subgroup of individuals with juvenile-onset Pompe disease, as it considered these younger individuals would likely gain more benefit from treatment.

11.15.2. The Committee noted alglucosidase alfa was considered standard of care worldwide and is publicly funded in many countries.

Health need

11.16. The Committee noted it had considered the health need of people with LOPD in November 2018.

11.17. The Committee noted LOPD is caused by a partial GAA enzyme deficiency (<30% residual activity) and may develop at any age from early childhood to late adulthood (mean age of symptom onset: 29 to 33 years) with a more variable clinical course and presentation (Al Jasmi et al, BMC Neurol. 2015:15:205). Individuals often present with musculoskeletal complications, such as limb girdle and axial weakness and respiratory insufficiency (Schoser et al, BMC Neurol. 2017;17:202; Toscano et al Ann Transl Med. 2019;7:284, Taverna et al, Aging (Albany NY). 2020;12:15856-74).

11.18. The Committee noted LOPD is generally not associated with cardiac hypertrophy, but other cardiac involvement may be present (Kronn et al, Pediatrics. 2017;140:S24-S45). LOPD is associated with progressive disease and significant morbidity resulting in poor health related quality of life (HRQoL) (Schoser et al, 2017). Over time, individuals may require wheelchairs to aid mobility and/or mechanical ventilation to aid breathing, and respiratory failure is the main cause of death (Schoser et al. 2017; Hagemans et al Brain. 2005;128(Pt 3):671-7, Winkel et al, J Neurol. 2005;252:875-84).

11.19. The Committee noted the median age of death observed in a cohort of 268 adults with LOPD was reported to be 55 years, with a median survival after diagnosis of 27 years (Güngör et al, Orphanet J Rare Dis. 2011:6:34). A review of 225 case reports of later onset Pompe disease (non-classic IOPD plus LOPD) from the scientific literature reported that of 36 patients who had died, 15 (41.7%) of those deaths occurred in patients less than 20 years of age (Winkel et al. 2005).

11.20. The Committee noted there are no specific treatments for LOPD funded in New Zealand and that there is a heavy reliance on participatory research and compassionate programmes to treat individuals. The Committee noted that there seven individuals with LOPD are receiving avalglucosidase alfa in New Zealand

through the Sanofi Humanitarian programme, whilst four additional individuals currently receive cipaglucosidase alfa/miglustat (AT-GAA) as part of a clinical trial.

11.21. The Committee noted supplier estimates that in New Zealand, one additional person would be diagnosed with Pompe disease every 2 years. The Committee considered LOPD could be underdiagnosed but there is a lack of data in the New Zealand setting. The increase in the use of gene panels in patients with muscle disease or unexplained elevated CK is increasing diagnostic rates.

11.22. The Committee noted Theadom et al. Neuroepidemiology. 2019;52:128-35 reported the estimated prevalence (per 100,000 (95% CIs) of Pompe disease in New Zealand was 0.24 (0.10–0.51, n=7) in New Zealand Europeans and 0.33 (0.06–1.35, n=2) in Māori.

11.23. The Committee noted a study of carers for people with Pompe disease in the Netherlands reported on average, caregivers provided 17.7 hours of informal care per week. Half of the informal caregivers reported mental health problems and problems with daily activities due to providing informal care. Physical health problems occurred in 40% of informal caregivers. Caregiver burden was higher if individuals with Pompe disease had a lower quality of life and/or were wheelchair dependent (Kanters et al. Mol Genet Metab. 2013;110:281-6).

Health benefit

11.24. The Committee noted the COMET phase 3 double-blind randomised trial, with crossover in the extension period, which recruited people with LOPD ≥3 years of age who were treatment naïve who were treated with 20 mg/kg avalglucosidase alfa or alglucosidase alfa every other week for 49 weeks then 20 mg/kg avalglucosidase alfa every other week.

11.24.1. The trial reported the following results at 97 weeks (Kishnani et al. JAMA Neurol. 2023;80:558-67):

- From baseline to week 97, least squares mean (LSM) (SE) upright forced vital capacity (FVC) percent predicted lung function increased by 2.65 (1.05) for avalglucosidase alfa and 0.36 (1.12) for switched to avalglucosidase alfa.
- The LSM 6-minute walk test (6MWT) distance increased by 18.60 (12.01) m and 4.56 (12.44) m, respectively.
- For those who switched to avalglucosidase alfa, FVC percent predicted remained stable (LSM change from week 49 to 97, 0.09 [0.88]) and 6MWT distance improved (LSM change from week 49 to 97, 5.33 [10.81] m).
- Potentially treatment-related adverse events (TRAE) were reported in 29 (56.9%) who continued avalglucosidase alfa and in 25 (56.8%) who switched.

11.24.2. The trial had previously reported the following results at 49 weeks (Diaz-Manera et al. Lancet Neurol. 2021;2:1012-26).

- Non-inferiority was shown (exceeded the predefined non-inferiority margin) but did not exclude 0 (p=0·0074). Superiority was not reached (p=0·063).
- TRAE potentially related to treatment were reported in 45% avalglucosidase alfa group vs 49% in alglucosidase alfa group.

11.25. The Committee considered the COMET trial data reported evidence of stability and some improvement in the clinical condition of people who participated. The Committee considered that stability in a condition with a declining clinical state was still an improvement compared to the overall trend to decline.

11.26. The Committee considered the trial endpoints were surrogate measures of clinical outcomes, and whilst percentage improvements were modest, these would be clinically meaningful to individuals with LOPD.

11.27. The Committee noted the NEO1 and NEO EXT, Phase 1, open-label, multicentre, multinational, ascending dose and extension in people with LOPD ≥18 years, receiving alglucosidase alfa naïve (naïve) or previously receiving alglucosidase alfa for ≥9 months (switch).

11.27.1. The trial reported the following results at 24 weeks (Pena et al. Neuromuscul Disord.2019;29:167-86) and 6.5 years (Dimachkie et al. Neurology. 2022;99:e536-48):

- Upright FVC% predicted remained stable in most participants, with slope estimates (95% CIs) of -0.473 per year (-1.188 to 0.242) and -0.648 per year (-1.061 to -0.236) in the naïve and previous-use groups, respectively.
- 6MWT% predicted was also stable for most participants, with slope estimates of -0.701 per year (-1.571 to 0.169) and -0.846 per year (-1.567 to -0.125) for naïve and previous-use groups, respectively.
- Improvements in 6MWT distance were observed in most aged <45 years at NEO1 enrolment in naïve and previous-use groups.

11.28. The Committee noted the Sarah et al. J Neurol. 2022;269:733-41 systematic review and meta-analysis including data from 589 individuals treated with alglucodisase alpha. The study reported the available data indicated that enzyme replacement therapy has a significant beneficial efficacy in the improvement of walking distance in LOPD patients and a non-significant improvement of muscle strength. No improvement in respiratory capacity was reported. The Committee considered overall trial data indicated avalglucosidase alfa may have superior health benefits when considering 6MWT in comparison to alglucosidase alfa, however the data was immature.

11.29. The Committee noted the following studies:

- Toscano et al Mol Genet Metab. 2024;141:108121.
- Dimachkie et al (2021). Molecular Genetics and Metabolism. 132:S34
- Schoser et al. J Neurol. 2017;264:621-30.
- Hahn et al. Genet Med. 2018;20:1284-94
- Nagura et al. Neurol Ther. 2019;8:397-409.
- Güngör et al. BMC Musculoskelet Disord. 2013;14: P15.
- Güngör et al. Orphanet J Rare Dis. 2011:6:34
- Winkel et al. J Neurol. 2005;252:875-84
- Carter et al. Front Genet. 2024:15:1309146
- Dalmia et al. Cochrane Database Syst Rev. 2023;12:CD012993

11.30. The Committee recalled its 2018 considerations that *"While recognising the challenges of generating high-quality data for rare conditions such as Pompe*

disease, the Subcommittee considered that the observational data set for LOPD did not provide a sufficient basis to demonstrate substantial life extension and there remains *significant uncertainty regarding treatment effect. Members considered the clinical benefits with regards to ambulation and pulmonary function are modest"*. The Committee however considered the new evidence discussed at the current meeting (May 2024) indicated that the reported improvements in clinical trial outcomes would be clinically meaningful in individuals with LOPD. The Committee further considered a reduction in clinical decline over time would be a major health benefit in people with LOPD.

11.31. The Committee accepted the view of the supplier applicant that avalglucosidase alfa has non-inferior efficacy and safety to alglucosidase alfa in LOPD, based on the Kishnani et al. 2023 COMET results.

11.32. The Committee considered there was a lack of long-term survival data for LOPD (associated with avalglucosidase alfa), which may become available in the next 5-10 years. Based on the current data the Committee considered it was uncertain how treatment affected overall survival.

11.33. The Committee considered the benefit of treatment with ERT in LOPD (avalglucosidase alfa or alglucosidase alfa) was highest when provided soon after disease onset. The Committee considered that some individuals may face delayed diagnosis, leading to progressive disability as the disease advances, and their potential to benefit from treatment decreases.

11.34. The Committee considered anecdotal evidence that following treatment with alglucosidase alfa, individuals initially report improvements, before reporting the disease had stabilised rather than continually improved. The Committee considered anecdotal evidence that whilst the length of health benefit from avalglucosidase alfa treatment is uncertain it may be longer lasting than alglucosidase alfa.

11.35. Overall, the Committee considered the evidence was of moderate to good strength and quality but had limited follow up data over time, similar to other rare disorder treatments.

Suitability

11.36. The Committee noted initial infusions must be provided in an infusion service setting, with each infusion lasting approximately 4-5 hours. If well tolerated further infusions can be received at home. The Committee considered infusion time would require individuals to take time away from paid work, as well as whānau.

Cost and savings

11.37. The Committee considered cross-reactive immunologic material (CRIM) status is less relevant to LOPD than to infantile onset Pompe disease (IOPD), as individuals with LOPD have residual native GAA enzyme activity and are less likely to have a vigorous immune response. Although antibodies towards treatment may be produced, it is less clear that efficacy of treatment is affected.

11.38. The Committee noted avalglucosidase alfa infusions would represent an increase in demand for infusion capacity for at least the first few infusions, which can take up to 4-5 hours to administer, every other week. The Committee considered this a significant burden on infusion services. The Committee noted infusions may be administered at home if there have been no infusion reactions, and individuals have received previous infusions under the supervision of a clinician.

11.39. The Committee considered there would be a reduction in pharmacy preparation time compared to alglucosidase alfa.

11.40. The Committee considered that if an individual's condition stabilises there may be less clinical need for respiratory clinic appointments, including non-invasive ventilatory support, thus providing a significant cost saving to respiratory services

11.41. The Committee noted that as dosing is weight-based, the cost of treatment would increase with the weight of the individual.

11.42. The Committee considered the health system burden of avalglucosidase alfa infusions was minimal in comparison to the necessary care for people with LOPD who are not treated.

11.43. The Committee considered it to be reasonable for economic modelling to assume that the overall survival (OS) benefit for alglucosidase alfa can be used as a proxy to estimate the OS benefit for avalglucosidase alfa, based on the assumption that avalglucosidase alfa is at least as effective as alglucosidase alfa.

11.44. The Committee considered there was a lack of data to determine the overall survival benefit of avalglucosidase alfa, and further long-term data is needed.

Summary for assessment

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

Population	Late onset Pompe disease with at least one of the following features: impaired respiratory function, sleep disordered breathing or significant clinical muscle weakness.
Intervention	Avalglucosidase alfa 20mg/kg IV every two weeks. Patients continue treatment until they no longer experience clinical improvement or stabilisation associated with treatment.
Comparator(s)	Placebo (standard of care)
Outcome(s)	The supplier claims that avalglucosidase alfa demonstrates non inferior efficacy and safety to alglucosidase alfa, based on the findings from COMET, in which the following outcomes were assessed: • Forced vital capacity (FVC) % predicted, • 6-minute walk test (6MWT), • Maximum inspiration pressure (MIP), • Maximum expiratory pressure (MEP) Based on this claim, the supplier has assumed any survival benefit with alglucosidase alfa may be used as a proxy for avalglucosidase alfa. A pooled analysis provided by the supplier indicates that in LOPD, the risk of death is reduced by 82% for individuals treated with alglucosidase alfa compared with natural history (HR 0.181; 95% CI: 0.11, 0.29).
Table definitions: Population, the target population for the pharmaceutical; Intervention, details of the intervention pharmaceutical; Comparator, details the therapy(s) that the target population would receive currently (status quo – including best supportive care); Outcomes, details the key therapeutic outcome(s) and source of outcome data.	