5.13 LANADELUMAB, Injection 150 mg in 1 mL single use pre-filled syringe, Takhzyro®, Takeda Pharmaceuticals Australia Pty. Ltd.

1 Purpose of submission

1.1 The Category 2 submission requested General Schedule Authority Required (Written) listing of a new form of lanadelumab for the preventative treatment of hereditary angioedema (HAE) Types 1 or 2 in patients aged 2 to 11 years.

1.2 The submission claimed superior effectiveness and inferior safety compared to on-demand treatment (ODT) with icatibant or C1 esterase inhibitor (C1-INH). The submission did not present an economic evaluation.

1.3 The key components of the clinical issue addressed by the submission are presented in Table 1.

Table 1 Key components of the clinical issue addressed by the submission (as stated in the submission)

Component	Description
Population	Patients diagnosed with HAE and aged 2 to less than 12 years who experienced at least one treated acute attack within a three-month period
Intervention[a]	Lanadelumab Patients aged 6 to <12 years 150 mg subcutaneously every 2 weeks. A dosing interval of 150 mg every 4 weeks may be considered if the patient is well controlled (e.g., attack-free) for 26 weeks. Patients aged 2 to <6 years 150 mg subcutaneously every 4 weeks
Comparator	SOC for HAE, which comprises use of ODT (icatibant or IV C1-INH)
Main outcomes	• HAE attack rate • HAE attack rate requiring acute treatment • Moderate or severe attacks • High-morbidity attacks • Attack-free patients • Safety
Clinical claim	Superior efficacy versus SOC
Economic	Cost-effectiveness of lanadelumab in this population cannot be quantified

Source: Table 1, p1 of the submission.
C1-INH = C1-esterase inhibitor; HAE = hereditary angioedema, ODT = on-demand treatment; SOC = standard of care
[a] Dosing regimen for lanadelumab added by the evaluation.

2 Background

Registration status

2.1 Lanadelumab 300 mg/2 mL solution in a pre-filled syringe was TGA registered in June 2020 "… for routine prevention of recurrent attacks of hereditary angioedema (C1-esterase-inhibitor deficiency or dysfunction) in patients aged 12 years and older".

2.2 Lanadelumab 150 mg/1 mL solution in a pre-filled syringe was TGA registered in July 2024 "… for routine prevention of recurrent attacks of hereditary angioedema (C1-esterase-inhibitor deficiency or dysfunction) in adult and paediatric patients aged 2 years and older".

2.3 The TGA Delegate's Overview for the 2024 registration stated "the number of patients in the SPRING study was very limited (n=21), however the cumulative efficacy and safety data in older patients and similar exposures demonstrated in paediatric patients compared to adult patients for the selected dosing regimens was supportive of registration."

Previous PBAC consideration

2.4 Lanadelumab was considered by the PBAC for prevention of attacks of HAE in patients aged ≥12 years in July 2019, July 2020, and again in July 2021.

2.5 Lanadelumab (300 mg/2 mL injection) is currently PBS-listed for the preventative treatment of HAE in patients aged 12 years and older. To be eligible under the existing

listing, patients must have experienced at least 12 treated acute attacks of HAE within a 6 month period prior to commencing lanadelumab.

2.6 Key points of the previous PBAC considerations that may be relevant to the present submission include:

- the listing of lanadelumab could not be justified without some criterion of frequency of attacks, noting that "the ICER was highly sensitive to the baseline HAE attack rate" (paragraph 6.7, lanadelumab Public Summary Document (PSD), July 2021).
- the PBAC noted stakeholder input that some patients who experience fewer attacks than the threshold number may have a high burden of disease because of the nature of the attacks. The sponsor indicated that it did not intend to propose quality of life or burden of disease criteria for eligibility "at this time" (paragraph 3.7, lanadelumab PSD, July 2021). The present submission also does not refer to quality of life or burden of disease criteria.

3 Requested listing

3.1 Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with strikethrough.

Name, form	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Proprietary name and manufacturer
lanadelumab 150 mg~~/~~ 1 mL ~~SC~~ injection~~, PFS~~, *1 mL syringe*	NEW MP	1	1	5	TAKHZYRO® TAKEDA Australia Pty Ltd

Initial treatment – New patient
Restriction Summary New/ ToC: New

Concept ID – for Dept. use	**Category / Program:** GENERAL – General Schedule (Code GE)
	Prescriber type: ☒ Medical Practitioners
	Restriction type: ☒ Authority Required (in writing only via post/HPOS upload)
	Administrative advice: No increase in the maximum number of repeats may be authorised.
	Administrative advice: Special Pricing Arrangements apply.
	Indication: Chronic treatment of hereditary angioedema Types 1 or 2
	Treatment Phase: Initial 1: New patient (commencing with no previous treatment with C1-INH for routine prophylaxis)
	Clinical criteria:
	Patient must have experienced at least one treated acute attack of hereditary angioedema within the 3 month period prior to commencing treatment with this drug
	AND
	Clinical criteria:
	Patient must not have been receiving a C1-esterase inhibitor through the National Blood Authority as routine prophylaxis for hereditary angioedema at the time of application
	AND
	Clinical criteria:
	The treatment must not be used in combination with a C1-esterase inhibitor concentrate
	AND
	Treatment criteria:
	Must be treated by a clinical immunologist or a specialist allergist
	Population criteria:
	Patient must be *aged* ~~at least~~ 2 – 11 years *inclusive* ~~of age~~
	Prescribing instructions: For the purposes of administering this restriction, acute attacks of hereditary angioedema are those of a severity necessitating immediate medical intervention with either (i) icatibant, or (ii) C1-esterase inhibitor concentrate.
NEW PI1	**Prescribing instructions:** The baseline measurement of the number of treated acute attacks of hereditary angioedema within the 3 months prior to initiating treatment must be provided at the time of submitting this application
	Administrative advice: *Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).* *Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au* *Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos* *Or mailed to:* *Services Australia* *Complex Drugs* *Reply Paid 9826* *HOBART TAS 7001*

Initial treatment – New patient coming from NBA-funded C1-INH
Restriction Summary New/ ToC: New

Concept ID – for Dept. use	**Category / Program:** GENERAL – General Schedule (Code GE)
	Prescriber type: ☒ Medical Practitioners
	Restriction type: ☒ Authority Required (in writing only via post/HPOS upload)
	Administrative advice: No increase in the maximum number of repeats may be authorised.
	Administrative advice: Special Pricing Arrangements apply.
	Indication: Chronic treatment of hereditary angioedema Types 1 or 2
	Treatment Phase: Initial 2: New patient (commencing from National Blood Authority-funded C1-INH)
	Clinical criteria:
	Patient must have been receiving a C1-esterase inhibitor through the National Blood Authority as routine prophylaxis for hereditary angioedema immediately prior to receiving lanadelumab
	AND
	Clinical criteria:
	The treatment must not be used in combination with a C1-esterase inhibitor concentrate
	AND
	Treatment criteria:
	Must be treated by a clinical immunologist or a specialist allergist
	Population criteria:
	~~Patient must be aged 2 years and older~~. *Patient must be aged 2-11 years inclusive*
	Administrative advice: *Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).* *Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au* *Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos* *Or mailed to:* *Services Australia* *Complex Drugs* *Reply Paid 9826* *HOBART TAS 7001*

While Table 17 of the submission proposed a new listing (for 'New patient coming from NBA-funded C1-INH'), the text in the submission and Table 5 of the Executive Summary indicated the submission requested a change to the existing listing only.

Initial treatment – New patient (Grandfather provision)
Restriction Summary New/ ToC: New

Concept ID – for Dept. use	**Category / Program:** GENERAL – General Schedule (Code GE)
	Prescriber type: ☒ Medical Practitioners
	Restriction type: ☒ Authority Required (in writing only via post/HPOS upload)
	Administrative advice: No increase in the maximum number of repeats may be authorised.
	Administrative advice: Special Pricing Arrangements apply.
	Indication: Chronic treatment of hereditary angioedema Types 1 or 2
	Treatment Phase: ~~Initial 2: New patient (Grandfather provision)~~ *Transitioning from non-PBS to PBS-subsidised treatment – Grandfather arrangements*
	Clinical criteria:
	Patient must have previously received non-PBS subsidised treatment with this drug *for this PBS indication* ~~as routine prophylaxis for HAE~~ prior to *[PBS listing date]* ~~[date to be determined]~~;
	AND
	Clinical criteria:
	Patient must have experienced at least one treated acute attack~~s~~ of hereditary angioedema within the 3-month period prior to commencing treatment with this drug *for this PBS indication*;
	AND
	Clinical criteria:
	The treatment must not be used in combination with a C1-esterase inhibitor concentrate
	AND
	Treatment criteria:
	Must be treated by a clinical immunologist or a specialist allergist
	Population criteria:
	Patient must be aged 2-11 years *inclusive*
	Prescribing instructions: For the purposes of administering this restriction, acute attacks of hereditary angioedema are those of a severity necessitating immediate medical intervention with either (i) icatibant, or (ii) C1-esterase inhibitor concentrate.
	Prescribing instructions: The baseline measurement of the number of treated acute attacks of hereditary angioedema within the 3 months prior to initiating *non-PBS subsidised* treatment *with this drug* must be provided at the time of ~~submitting~~ this application
	Administrative advice: *This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria.*
	Administrative advice: *Patients may qualify for PBS-subsidised treatment under this restriction once only per eye. For continuing PBS-subsidised treatment, a 'Grandfather' patient must qualify under the 'Continuing treatment' criteria.*
	Administrative advice: *Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).* *Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au* *Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos* *Or mailed to:* *Services Australia* *Complex Drugs* *Reply Paid 9826* *HOBART TAS 7001*

Continuing treatment
Restriction Summary New/ ToC: New

Concept ID – for Dept. use	**Category / Program:** GENERAL – General Schedule (Code GE)
	Prescriber type: ☒ Medical Practitioners
	Restriction type: ☒ Authority Required (~~in writing only via post/HPOS upload~~ *telephone/online immediate assessment*)
	Administrative advice: No increase in the maximum number of repeats may be authorised.
	Administrative advice: Special Pricing Arrangements apply.
	Indication: Chronic treatment of hereditary angioedema Types 1 or 2
	Treatment Phase: Continuing preventative treatment
	Clinical criteria:
	Patient must have previously received PBS-subsidised treatment with this drug for this condition
	AND
	Clinical criteria:
	Patient must have demonstrated or sustained an adequate response to PBS-subsidised treatment with this drug for this condition
	AND
	Clinical criteria:
	The treatment must not be PBS subsidised in combination with a C1-esterase inhibitor concentrate
	AND
	Treatment criteria:
	Must be treated by a specialist allergist or clinical immunologist, or in consultation with a specialist allergist or clinical immunologist
	Population criteria:
	~~Patient must be aged 2 years and older~~. *Patient must be aged 2-11 years inclusive*
	Prescribing instructions: Patients who have successfully transitioned to a lower dosing frequency should be reviewed every 6 months to ensure they continue to demonstrate a sustained response
	Prescribing instructions: For the purposes of administering this restriction, an adequate response is a reduction of the baseline number of acute attacks of hereditary angioedema of a severity necessitating immediate medical intervention with either (i) icatibant, or (ii) C1-esterase inhibitor concentrate. The details of the reduction must be documented in the patient's medical records for auditing purposes
	Administrative advice: *Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday)*

3.2 The submission requested listing of a 150 mg/1 mL formulation in patients aged 2 to 11 years who experience at least one treated acute attack of HAE within the 3-month period prior to commencing lanadelumab. This was revised to at least 2 treated attacks within 6 months in the Pre-Sub-Committee Response (PSCR).

3.3 The submission proposed 4 restrictions: initial and continuing treatment for patients aged 2-11 years; a grandfathering restriction for patients currently receiving treatment through a special access program; and an amendment to the existing restriction for new patients commencing from National Blood Authority-funded C1-INH to incorporate patients aged 2 years or older.

3.4 The evaluation noted the following points regarding the proposed restriction:

- The existing listing for lanadelumab in patients aged ≥12 years requires patients to have experienced ≥12 attacks in the preceding six months; the PBAC previously considered that a threshold attack frequency was required to make listing cost-effective in patients aged ≥12 years (paragraphs 7.3 and 7.5, lanadelumab PSD, July 2021). The PSCR stated that it would not be clinically appropriate to wait for a child to experience 12 attacks in 6 months before accessing an effective prophylaxis (further discussed in paragraphs 3.6 and 3.7).
- The SPRING trial, on which the submission relied, required a history of at least one attack per 3 months and at least one attack in the 3 months directly preceding commencement of lanadelumab treatment. The amended restriction proposed in the PSCR (2 treated attacks in the 6 months prior to treatment initiation) is consistent with the SPRING trial patient population.

3.5 The evaluation and the ESC considered that as treatment is usually continued indefinitely, the proposed restriction may create issues of equity between two populations of patients aged over 12 years receiving ongoing treatment: those who initiated treatment at ages ≥12, satisfying the requirement for at least 12 attacks in the preceding six months; and those who initiated treatment aged <12, satisfying the requirement for only one attack in the preceding three months. The evaluation and the ESC noted that between 25% and 50% of patients with HAE who are aged ≥12 years have 12 or more attacks in a 6 month period and are eligible under the existing criterion, but nearly all children who are diagnosed with HAE before the age of 12 would be eligible under the submission's proposed criterion of one attack in 3 months.

3.6 The PSCR maintained that a lower attack rate is warranted in the 2-11 year old population. The PSCR stated "given that these paediatric patients [experiencing HAE attacks before the age of 12] represent early onset disease, they would likely qualify for treatment under the adolescent/adult criteria in the future", and the proposed listing "will, by virtue of the early onset of disease, target a clinically relevant and severe phenotype of HAE without the distress and burden of enduring multiple attacks associated with the existing listing for adolescents and adults." The PSCR cited a survey (conducted by the United States HAE Association) of 581 adult patients with a history of physician-confirmed HAE (Christiansen 2016[1]). The publication stated that "Earlier onset of symptoms correlated with longer delays in diagnosis (P <0.001) and predicted a more severe disease course, including increased number of attacks per year (P = 0.0009) and hospital admissions (P = 0.009). Earlier age of onset also significantly correlated with increased perceived HAE severity (P = 0.0002), negative overall life impact (P <0.0001), and use of anabolic androgen."

3.7 The ESC considered that while there may be a link between early onset disease and severity, the submission had not presented strong evidence to indicate that patients

[1] Christiansen et al, Pediatric Hereditary Angioedema: Onset, Diagnostic Delay, and Disease Severity. *Clinical Pediatrics* 2016;55(10):935-942.

who experience 1 attack at <12 years of age are likely to experience ≥12 attacks in 6 months when they are ≥12 years of age. The ESC considered that, in the absence of evidence to support the proposed lower baseline attack frequency in patients aged 2-11 years, it would be appropriate to expand the current restriction to be age agnostic i.e. with the same criteria around baseline attack frequency. While the Pre-PBAC response acknowledged the lack of evidence due to the rarity of the condition, it stated that requiring ≥12 attacks in 6 months may result in no appreciable improvement in access to lanadelumab for the paediatric population due to no patients <12 years meeting this attack frequency threshold.

3.8 The TGA Product Information outlines that the recommended dosage is 300 mg every 2 or 4 weeks in patients aged ≥12 years and 150 mg every 2 or 4 weeks in patients aged <12 years (with the dosing interval dependent on other patient criteria). Only the 300 mg presentation is currently PBS-listed. The ESC considered that both presentations should be listed age agnostically if the PBAC were to recommend access for patients aged <12 years.

3.9 The Pre-PBAC response requested that if the PBAC prefers an age agnostic listing, the grandfather provision should allow for patients on the current access program (based on the proposed restriction including a baseline attack rate of one attack in 3 months) to move onto PBS supply.

3.10 The submission proposed that the effective and published prices for the 150 mg injection should be the same as the current prices for the 300 mg strength.

For more detail on PBAC's view, see section 7 PBAC outcome.

4 Population and disease

4.1 HAE is an uncommon disease characterised by recurrent episodes of swelling. Prevalence estimates range from 1/10,000 to 1/150,000, clustering around 1/60,000 individuals. Males and females are affected equally, and there are no identified differences among ethnic groups. It should be noted that a prevalence of 1/60,000 would imply that there are about 500 patients with HAE in Australia, and even the lowest estimated prevalence would imply 200. The database of the Australian Society of Clinical Immunology and Allergy has only 66 patients, so there appears to be substantial under-reporting.[2]

4.2 In most cases, HAE is due to gene mutations causing deficiency ("Type I", 85% of cases) or dysfunction ("Type II", 15% of cases) of C1 inhibitor (C1-INH); these cases are designated HAE – C1-INH. Reduced C1-INH function results in episodes of uncontrolled production of bradykinin, leading to local increases in vascular permeability and oedema, and to low levels of C4, which is not related to pathogenesis but is a sensitive

[2] https://www.allergy.org.au/images/docs/ASCIA_HP_Position_Paper_HAE_2022_Updated_Nov.pdf accessed 24 August 2024.

and readily available diagnostic test. HAE – C1-INH displays autosomal dominant inheritance and most patients have a positive family history.

4.3 The first attack occurs before age 5 years in 40% of patients and before age 15 years in 75% of patients, but diagnosis is often delayed, especially if there is no family history and attacks are infrequent. The submission stated: "while approximately 50% of those with HAE suffer their first attack before the age of 10 years, the diagnosis of HAE is usually not made until the second or third decade of life. Studies have documented an average delay to diagnosis of 13 to 21 years despite improvements in screening and general awareness of HAE. Consequently, relatively few patients are diagnosed with HAE below the age of 12 years."

4.4 Attacks can be spontaneous, or precipitated by medications or medical or dental procedures. Attacks are unpredictable, and the frequency of attacks varies from one or two episodes per year to more than one per week. In one series of 226 HAE patients followed for up to 19 years, 2% had never had an attack, 26% had <1 attack per year, 23% had between 1 and 5 attacks per year, 16% had between 6 and 12 attacks per year, and 30% had over 12 per year. The submission stated that attacks are generally both less frequent and less severe before puberty than after.

4.5 Attacks can affect the skin (most often the hands, feet, and face), the upper airway, or the gastro-intestinal tract. Attacks develop over several hours, and are always self-limiting, usually lasting about two days. Attacks affecting the upper airway can be life-threatening. Although severe attacks are less common in young children, their airway is smaller and they may be at higher risk. In the largest reported series of deaths from laryngeal attacks in HAE, 63/70 (90%) occurred in undiagnosed patients. One of 70 deaths occurred in a child aged less than 16 years. The overall risk of death from laryngeal attacks in patients known to have HAE was 1.1 (95% CI: 0.4, 2.3) per 1000 patients.[3]

4.6 Patients are often unable to work or attend school during an attack. In a cross-sectional study of 164 adult patients identified through registries in Germany, Spain and Denmark, the median (range) number of attacks per year was 12.0 (1.0-156.0), the median (range) days of work or education lost in the most recent attack was 0.25 (0-8.0), and the median (range) number of days lost in the past year was 8.0 (0-210.0).[4] The principal determinant of absenteeism was attack frequency, and patients with frequent attacks were more likely to report difficulty staying in work or reaching their educational potential.

[3] Bork K, Hardt J, Witzke G. Fatal laryngeal attacks and mortality in hereditary angioedema due to C1-INH deficiency. *J Allergy Clin Immunol* 2012; 130:692-7.

[4] Aygoren-Pursun E, Bygum A, Beusterien K, et al. Socioeconomic burden of hereditary angioedema: results from the hereditary angioedema burden of illness study in Europe. *Orphanet J Rare Dis* 2014; 9:99-108.

4.7 There are two broad approaches to treatment of HAE: ODT when attacks occur, and continuous treatment to prevent attacks. Short-term prophylaxis with intravenous C1-INH is used for medical or dental procedures likely to precipitate attacks in patients using ODT.

4.8 ODT can be with icatibant, which blocks the action of bradykinin on its receptor, or with intravenous C1-INH. ODT administered by patients or carers as soon as an attack begins substantially reduces the severity and duration of the attack. Icatibant is given by subcutaneous injection and C1-INH for ODT by intravenous infusion. The volume of injections of icatibant is relatively large (1 mL up to 25 kg body weight, 1.5 mL 26-40 kg, 2 mL 41-50 kg, and 2.5 mL 51-65 kg), and it may be difficult to administer to younger children. Sebetralstat, an orally-administered inhibitor of plasma kallikrein, and deucrictibant, an orally-administered bradykinin receptor antagonist, have recently been reported to be effective for ODT.[5] However, these treatments are not available in Australia.

4.9 Preventative treatment can be C1-INH, given by subcutaneous rather than intravenous injection, or lanadelumab (or berotralstat, an orally-administered inhibitor of plasma kallikrein, which is approved in the USA for preventative treatment in HAE but is not registered in Australia).

4.10 Indications for preventative treatment are not well-defined. Important factors entering into the decision to start preventative treatment are the impact on the patient's quality of life, determined mainly by the frequency of attacks; whether patients or carers can administer ODT, or, if they cannot, whether they have rapid access to a health-care facility where ODT can be administered; the effectiveness of ODT for an individual; the perceived burden of preventative treatment relative to ODT; and uncertainty about the long-term safety of lanadelumab.[6] As a result, the proportion of patients who receive preventative treatment varies widely among treatment centres.[7] The use of preventative treatment does not eliminate use of ODT, because patients still require ODT in the event of breakthrough attacks. Once preventative treatment is begun and found to be effective, it is continued indefinitely (paragraph 3.6, lanadelumab PSD, July 2021).

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[5] Riedl M, Farkas H, Aygoren-Pursun E, et al. Oral sebetralstat for on-demand treatment of hereditary angioedema attacks. *N Engl J Med* 2024; 391:32-43; Riedl M, Aygoren-Pursun E, Cohn D, et al. Deucrictibant immediate-release capsule reduces time to end of progression of hereditary angioedema attacks' manifestations. *Ann Allergy Asthma Immunol* 2023, Supplement 1, pS38.

[6] https://www.allergy.org.au/images/docs/ASCIA_HP_Position_Paper_HAE_2022_Updated_Nov.pdf accessed 24 August 2024.

[7] For example, the UptoDate article on preventative treatment of HAE has two expert authors, of whom one has 70% of their patients on preventative treatment and the other has 20% of their patients on preventative treatment (https://www.uptodate.com/contents/hereditary-angioedema-due-to-c1-inhibitor-deficiency-general-care-and-long-term-prophylaxis?source=related_link#H9 accessed 15 July, 2024).

4.11 Lanadelumab binds to and inhibits plasma kallikrein, preventing the cleavage of high-molecular weight kininogen and the generation of bradykinin. Lanadelumab does not inhibit the tissue kallikrein-kinin system. This is believed to be important because of the role of bradykinin in vasomotor tone and endothelial function, but long-term adverse effects of lanadelumab arising from reduced activity of tissue bradykinin are possible, and this uncertainty is a factor in balancing long-term prophylaxis against ODT. Absorption after subcutaneous injection is slow and the elimination half-life is 15 days, so steady-state activity is reached only after 2 months with 2- or 4- weekly injections.[8]

For more detail on PBAC's view, see section 7 PBAC outcome.

5 Comparator

5.1 The ESC considered that the nominated comparator, ODT with either icatibant or intravenous C1-INH, was appropriate. This comparator was accepted by the PBAC in its previous considerations of lanadelumab in adults and adolescents (paragraph 7.6, lanadelumab PSD, July 2020). Preventative use of C1-INH would also be an alternative comparator, but the PBAC previously considered that, as this use is confined to patients experiencing eight or more attacks per month, ODT was appropriate as the comparator for the lanadelumab-eligible population as a whole (paragraphs 5.2 and 5.3, lanadelumab PSD, July 2021). In the clinical section of the current submission, the number of attacks in the baseline observation period was used as the point of comparison, as a proxy for ODT use.

5.2 The PBAC considered a submission for garadacimab, an inhibitor of activated Factor XII, at its November 2024 meeting. The submission "request[s] a General Schedule Authority Required (Written) listing for the initial treatment and an Authority Required (Telephone/Online) listing for the continuing treatment of HAE". The completed efficacy trial of garadacimab enrolled patients 12 years of age or older.[9] A study of garadacimab in children aged 2 to 11 years (NCT05819775) is underway and scheduled for completion in late 2026.[10] Garadacimab could therefore be considered a near-market comparator.

For more detail on PBAC's view, see section 7 PBAC outcome.

[8] Wang Y, Marier J-F, Kassir N, Chang C, Martin P. Pharmacokinetics, pharmacodynamics, and exposure-response of lanadelumab for hereditary angioedema. *Clinical & Translational Science* 2020, https://doi.org/10.1111/cts.12806

[9] Craig TJ, Reshef A, Li HH, et al. Efficacy and safety of garadacimab, a Factor XIIa inhibitor for hereditary angioedema prevention (VANGUARD): A global, multicentre, randomised, double-blind, placebo-controlled, phase III trial. *Lancet* 2023; 401:1079-1090.

[10] https://clinicaltrials.gov/study/NCT05819775?term=garadacimab&rank=3 accessed 6 August, 2024.

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted and welcomed the input from individuals (2), and health care professionals (2). The comments described a range of benefits of treatment with lanadelumab including improved quality of life, avoidance of acute hospital presentations, and lower frequency of needle insertions (compared to other long term prophylactic options).

6.3 A health professional noted that treatment of most paediatric patients is usually based on ODT, with relatively low use of long-term prophylactic (LTP) therapies prior to puberty. They noted that some paediatric patients with a more severe phenotype do require LTP based on attack frequency and severity (e.g. laryngeal involvement), but that as lanadelumab preventative treatment requires ongoing subcutaneous injections (albeit less than other LTP options), decisions for treatment are not taken lightly.

6.4 Another health professional noted that young children with genetic and biochemical markers for HAE may not require prophylaxis because HAE attacks are generally very infrequent before puberty; however there are exceptions of children who suffer reasonably frequent attacks. The health professional advised that suitable LDP options should be available to these patients, to avoid adverse occurrences including the potentially traumatic requirement to attend hospital for treatment with IV C1-INH, unnecessary surgery associated with recurrent abdominal pain, and dangerous and potentially fatal laryngeal attacks associated with angioedema.

6.5 An individual who previously used lanadelumab noted it was more effective than other preventatives including danazol, which the PBAC noted is no longer available in Australia, and Berinert (C1-INH), and has been attack free while on lanadelumab. Another individual wanting to access lanadelumab noted that the requirement for lanadelumab to be refrigerated makes travel difficult.

Clinical trials

6.6 The submission was based on one single-arm, open label study of lanadelumab (SPRING). This study was designed to evaluate the safety and pharmacokinetics of lanadelumab in patients with HAE aged 2-11 years; assessment of attack rate was a secondary objective. Changes in health-related quality of life were an exploratory objective.

6.7 Details of the trial documents and related publications are provided in Table 2.

Table 2: Trials (and associated reports) presented in the submission

Trial ID	Protocol title/publication title	Publication citation
SPRING (NCT04070326)	Lanadelumab in patients 2 to less Than 12 Years old with hereditary angioedema: Results from the Phase 3 SPRING study.	CSR, August 2021
Maurer et al 2024	Maurer, M. et al. Lanadelumab in patients 2 to Less Than 12 years Old With Hereditary angioedema: Results from the Phase 3 SPRING study.	Journal of Allergy and Clinical Immunology: In Practice 2024 12(1): 201-211.e206.
Lumry et al 2023	Lumry, W., et al. Efficacy of lanadelumab at fixed and modified dosing regimens in patients aged 2 to <12 years old with hereditary angioedema (HAE) in the Phase 3, open-label, multicenter SPRING study." Conference abstract	Journal of Allergy and Clinical Immunology 2023 151(2): AB140.
Watt et al 2023	Watt, M., et al. "Health-related Quality of Life (HRQoL) in pediatric patients with hereditary angioedema (HAE) receiving lanadelumab: Exploratory results from the SPRING study. Conference abstract	Journal of Allergy and Clinical Immunology 2023 151(2): AB139.

Source: Table 21, p23 of the submission.
CSR = clinical study report.

6.8 The key features of the SPRING study are summarised in Table 3.

6.9 As discussed in paragraph 3.4, patients in the SPRING trial required a history of at least one attack per 3 months and also at least one attack in the 3 months directly preceding commencement of lanadelumab treatment. While patients were required to have "a history of ≥1.0 angioedema attacks per 3 months", it was not stated whether this was to be a long-term average or a highest observed frequency. Patients meeting this criterion stopped preventative treatment and entered an observation period of at least 4 weeks and up to 12 weeks. Those who reported an attack within the first four weeks entered the lanadelumab treatment phase at 4 weeks, and those who recorded an attack after 4 weeks entered the lanadelumab treatment phase as soon as the attack occurred. Those who had two attacks within the first two weeks of the observation period could begin lanadelumab immediately.

6.10 Attacks during the observation period were used to calculate a rate that was used as the baseline for the study, but barring patients who had multiple attacks before completing four weeks of the observation period, the rate was based on a single attack. That is, a patient who had an attack at 3 weeks would be recorded as having a baseline attack rate of 1.3/month, a patient who had an attack at 4 weeks would be recorded as have a rate of 1/month and a patient who had an attack at 8 weeks would be recorded as having a baseline attack rate of 0.5/month.

6.11 This method requires the assumption that if a patient had an attack early in the observation period, they would have gone on to have repeated attacks at the same rate. The evaluation considered that this assumption is unlikely to be valid. The unpredictability of attacks of HAE is a prominent feature of the disease that impairs quality of life. A fall in the attack rate with time is particularly likely where a threshold attack rate is required for entry to the study. In the HELP trial of lanadelumab vs placebo in adult and adolescent patients with HAE, the mean attack rate in the placebo

group was 4 attacks per month at baseline, but less than 2.5 attacks per month in month 3; 31.7% of patients in the placebo group had a reduction in attack rate of 50% or more from baseline and 2.4% of placebo-treated patients were attack free throughout the 26 week treatment period.[11]

6.12 Patients aged 2-5 years were to receive lanadelumab 150 mg every 4 weeks (Q4W) and patients aged 6-12 lanadelumab 150 mg every 2 weeks (Q2W). These doses were chosen on pharmacokinetic grounds, to provide similar exposure to 300 mg Q2W, the dose for adolescents and adults. Patients aged 6-12 who were well-controlled after 26 weeks could change to 150 mg Q4W.

6.13 Although long-term preventative treatment was stopped at the beginning of the baseline period, short-term prophylaxis with C1-INH, androgens or antifibrinolytics was allowed for medical or dental procedures. Such procedures were reported for 7/21 (33.3%) patients but the number for which short-term prophylaxis was used was not reported.

Table 3: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
SPRING	21; 4 were aged 2-5 years and 17 were aged 6-12 years	SA, OL, 52 weeks	High[a]	Aged 2-12 years, HAE, ≥ 1 attack per 3 months and ≥ 1 attack in observation period up to 12wk with no LTP; patients aged 2-5 received 150 mg Q4W for 52 wks; patients aged 6-12 received 150 mg Q2W for 26 wks, then if well-controlled could switch to 150 mg Q4W for 26 wks	Safety (primary outcome); number of attacks in 52 wk treatment period	Not used

Source: Figure 6, Table 22, pp24-27 of the submission.
HAE = hereditary angioedema; LTP = long term prophylaxis; OL = open label; Q4W = every 4 weeks; Q2W = every 2 weeks; SA = single arm; wks = weeks.
[a] High risk of bias for efficacy outcomes as there was no comparator, unblinded outcomes, no control of time varying cofounding due to change in baseline rate, no control of confounding due to recall bias in establishing baseline rate.

6.14 As described in Table 3, the primary outcome for the study was safety, with efficacy as a secondary outcome. The mean (standard deviation) number of attacks in the preceding 12 months was 15.5 (14.5), which, as expected, is much lower than the mean number of attacks observed in the standard-of-care arm of the HELP trial (54.8/patient year; paragraph 6.8, lanadelumab PSD, July 2021), since HAE attacks generally become more frequent after puberty (paragraph 4.4). It was also lower than the number of attacks required for PBS eligibility for lanadelumab in adults and adolescents (12 in six months). During the baseline period, 5/21 (23.8%) patients in

[11] Banerji A, Riedl MA, Bernstein JA, et al. Effect of lanadelumab compared with placebo on prevention of hereditary angioedema attacks: A randomized clinical trial. *JAMA* 2018; 320:2108-2121.

the SPRING trial were recorded as having a baseline attack rate ≥2 attacks per month, but because of the way baseline attack rate was defined, this does not mean that they would have satisfied the PBS eligibility criterion of 12 attacks in 6 months.

6.15 In the SPRING trial, laryngeal attacks were reported in 5/21 (23.8%) patients and were reported to be the primary form of attack in 1/21 (4.8%). The Clinical Study Report (CSR) did not state criteria for diagnosis of laryngeal attacks and no information on the severity of the attacks (e.g., need for hospitalisation or for intubation) was provided.

6.16 The majority of patients (16/21, 76.2%) were not receiving preventative treatment at the screening visit. A substantial minority (5/21 = 23.8%) were not receiving the standard of care for ODT of either C1-INH or icatibant, and of the 16 who had received ODT, only three (14.3%) had received icatibant. The evaluation considered this to be important because:

> (a) the number of patients receiving a prescription for icatibant is used by the submission to estimate the number of potential users of lanadelumab (paragraph 6.36), and
>
> (b) it is difficult to reconcile not using prophylaxis or ODT with the submission's argument that the eligibility criterion for older patients should not be used for those aged 2-11 because "it would not be considered appropriate to wait for a patient aged between 2-11 years of age to experience 12 attacks in 6 months".

Comparative Effectiveness

6.17 The efficacy results of the SPRING study are shown in Table 4.

Table 4: Efficacy outcomes in the SPRING study

	Lanadelumab N = 21	Baseline Observation Period[a] N = 21
Attacks/month		
All Attacks, Mean, (SD) Median (range)	 0.08 (0.170) 0.00 (0.0 - 0.5)	 1.84 (1.525) 1.44 (0.6 - 6.7)
Moderate or Severe Attacks Mean (SD) Median (range)	 0.08 (0.160) 0.00 (0.0 - 0.5)	 1.27 (1.286) 0.88 (0.0 - 5.0)
High-Morbidity Attacks[b] Mean (SD) Median (range)	 0.01 (0.034) 0.00 (0.0 - 0.2)	 0.16 (0.304) 0.00 (0.0 - 0.8)
Patients with no attacks, n (%)	16 (76.2%)	NA
Patients with attacks, n (%)	5 (23.8%)	NA
Number of attacks	23	NR
Achieved MCID for change in PedsQL, n/N, %		
Aged 2-4	2/2 (100%)	NA
Aged 5-7	4/5 (80%)	NA
Aged 8-11	9/13 (69.2%)	NA
Rescue medication, occasions of use during treatment period		
Icatibant	6	5
C1-INH	14	38

Source: Table 30, p37, Table 32, p41, Table 33, p43, Table 34, p44, Figure 8, p45, Table 36, p47 of the submission; Table 12, p97, Table 18, p105, Table 22, p110, Table 25, pp120-4, SPRING CSR.

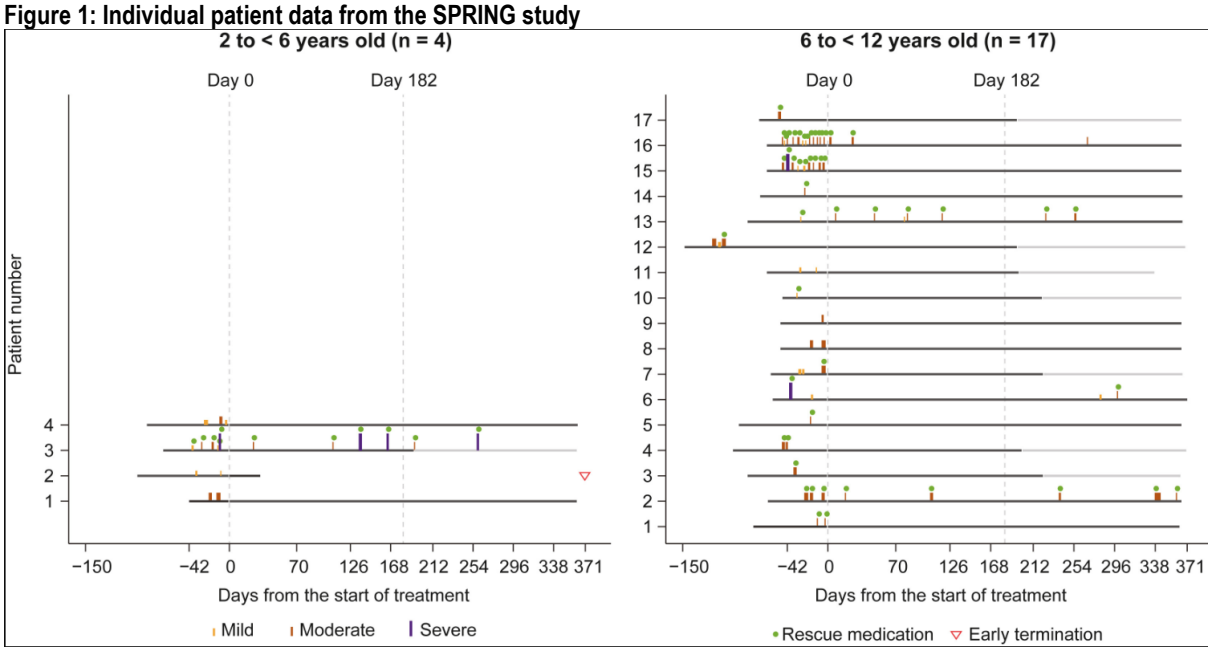
MCID = minimum clinically-important difference; NA = not applicable; NR = not reported; PedsQL = paediatric quality of life inventory; SD = standard deviation.

[a] Up to twelve weeks duration, but patients were observed only until an attack occurred, then entered the treatment period, except for attacks in the first 4 weeks, except that patients having 2 attacks in the first 2 weeks could enter the treatment period immediately; preventative treatment, if used, was ceased at the start of the observation period.

[b] A high-morbidity attack was any attack that: was severe; resulted in hospitalization (except hospitalization for observation <24 hours); was hemodynamically significant (systolic blood pressure <90 or required IV hydration or was associated with syncope or near-syncope); or was laryngeal (SPRING CSR, p56).

6.18 The number of HAE attacks was reduced by treatment with lanadelumab. The evaluation considered that it was difficult to compare the on-treatment rates with the baseline rates because of the way the baseline rate was defined (see paragraphs 6.10 and 6.11). The study results are shown graphically in Figure 1. This shows attacks for individual patients during the study, by original treatment assignment. The horizontal line is marked grey after the patient's dose regimen changed. Only attacks that occurred during the baseline observation and treatment periods are depicted. During the fixed dosing period (Day 0 to 182), 4/21 patients reported 13 attacks. After this (when dosing could be adjusted to Q4W in patients over 6 years, paragraph 6.12), 5 patients reported 10 attacks and 15 patients were attack free.

Figure 1: Individual patient data from the SPRING study



Source: Figure 3, p 208, Maurer et al 2024.
Note: Patient 17 had one attack after the baseline observation period and before administration of the first dose (the attack is not depicted).

6.19 Moderate-to-severe attacks and high-morbidity attacks were also fewer on treatment, but there were few events both on-treatment and during the baseline observation period.

6.20 The majority of patients (16/21, 76.2%) were attack-free on treatment. The five patients who had attacks had a total of 23 attacks over the 52 weeks treatment period, fewer than the historical average for the group as a whole, but not necessarily for those individual patients.

6.21 Quality of life scores using PedsQL improved to a meaningful extent in the majority of patients although this may have been less apparent in the older children in the trial (Table 4). The evaluation considered that it is difficult to interpret this finding in the context of a single-arm unblinded trial with small numbers.

Comparative Harms

6.22 Adverse events from the SPRING study are shown in Table 5.

Table 5: Treatment-emergent adverse events

	N = 21	
	Number of patients reporting events (%)	**Number of events**
Any TEAE	17 (81.0)	210
Any treatment-related TEAE	7 (33.3)	121
Injection site pain	6 (28.6%)	88
Injection site erythema	3 (14.3%)	29
Infections and infestations	11 (52.4%)	18
Any serious TEAE	0	0
Any treatment-related serious TEAE	0	0
Any severe TEAE	1 (4.8)	20
AESI	0	0
Deaths due to TEAE	0	0
Hospitalisation due to TEAE	0	0
Study discontinuation due to TEAE	0	0

Source: Table 35, p46, Table 37, p48 of the submission.
AE, adverse event; AESI, adverse event of special interest (hypersensitivity reactions and events suggesting disordered coagulation); TEAE, treatment-emergent adverse event.

6.23 Adverse events were common, mostly accounted for by injection site reactions. The 20 severe TEAE reported by one patient were injection site reactions.

6.24 Infections and infestations have been identified as a common serious adverse event in clinical trials of lanadelumab. Eighteen infections were reported as adverse events in the SPRING trial, but apart from nasopharyngitis (3 events), rhinitis (3 events) and upper respiratory tract infection (2 events), all reported infections were single events and none were classified as serious.

Benefits/harms

6.25 Data from the single arm open label trial presented in the submission did not allow for a comparison of the benefits and harms of lanadelumab and ODT. Accordingly, a benefits/harms table has not been presented.

Clinical claim

6.26 The submission described lanadelumab as superior in terms of effectiveness compared with ODT with icatibant or C1-INH. Taking the evidence as a whole, the evaluation considered that it was reasonable to conclude that lanadelumab reduces the frequency of attacks in children below the age of 12 years, although the effect size is highly uncertain. The evaluation considered that the evidence in children aged <12 years does not support a claim that preventative treatment with lanadelumab is superior to ODT in terms of morbidity or quality of life, regardless of the frequency of attacks. However, the PSCR noted that patients "treated with lanadelumab demonstrated improvements in PedsQL Total Score, PedsQL-FIM Total Score and EQ-5D VAS score" (Table 4), and claimed that "[t]he SPRING trial, does therefore, provide the evidence to support the listing of lanadelumab in the paediatric population".

6.27 The PBAC agreed with the ESC that while the magnitude of benefit was unclear, the available data suggest that lanadelumab has superior efficacy in terms of preventing attacks, compared with ODT with icatibant or C1-INH. The ESC considered that it is

unlikely that new clinical data will become available in this very small population. Further, there is no mechanistic reason to assume that lanadelumab would be less (or more) efficacious in the different age groups, so previous data (from patients aged ≥12 years) was likely to support extending the existing listing to patients aged 2-11 years. However, the PBAC and the ESC considered that the submission had not presented strong evidence that patients who experience 1 attack [or 2 attacks according to PSCR update] within 6 months at <12 years of age are likely to experience ≥12 attacks within 6 months when they are ≥12 years of age.

6.28 The submission described lanadelumab as inferior in terms of safety compared to ODT with icatibant or C1-INH. The PBAC agreed with the evaluation and the ESC that this claim was reasonable, but very little relevant data were presented.

Economic analysis

6.29 The submission did not present an economic evaluation, stating that "there is insufficient data to populate an informative economic evaluation for lanadelumab in the proposed paediatric population." The submission acknowledged the limited data on the baseline frequency of HAE attacks in the requested population.

6.30 The submission requested listing of the 150 mg injection at the same price per vial as the currently-listed 300 mg strength for the ≥12 year population. However, the evaluation considered that it was unclear whether:

- the cost-effectiveness in the proposed population would be the same as in the existing population, given the proposed restriction for children is based on a lower baseline attack frequency. This parameter was a key driver of the economic model in adults (paragraph 6.7, lanadelumab PSD, July 2021).
- lanadelumab would have the same incremental clinical effect and impact on quality of life in children as in adults. However, the PBAC agreed with the ESC that there was no mechanistic reason to assume that the incremental effectiveness of lanadelumab would vary by patient age.
- this would result in the same price per patient per month, given the potential for differences in dosing frequency between children and adults. In the lanadelumab Product Information, the recommended starting dose in adults is 300 mg Q2W, with Q4W administration considered for patients who are well controlled (i.e. attack free) on treatment. This is similar to the dosing information for patients aged 6 to 11 years (albeit with 150 mg dosing), though the Product Information specifies a 26-week period of being well-controlled prior to reducing the dosing frequency in this age group. (The dose in patients aged 2 to 5 years is 150 mg Q4W.) It is unclear whether reductions in dosing frequency would occur to the same extent in children aged 6 to 11 years as in adults.

6.31 The submission proposed that extension of listing to the 2-11 years population would be cost-neutral to government because of "low expected utilisation, and […] the % rebate in place once the cap is reached", given the expenditure caps for the risk

sharing arrangement (RSA) for the 300 mg strength in patients ≥12 years are currently being exceeded.

6.32 The ESC considered that, regardless of the existing RSA, an economic evaluation would be required to support a lower baseline attack rate than the existing restriction for patients aged ≥12 years, given the previous economic evaluation was highly sensitive to this parameter (paragraph 6.7, lanadelumab PSD, July 2021).

Drug cost/patient/year

6.33 The cost per patient per year based on the effective price of lanadelumab is shown in Table 6. The submission essentially assumed a nil cost [to government] per patient per year if lanadelumab usage continues to exceed the subsidisation caps.

Table 6: Drug cost per patient per year for lanadelumab

	Every 4 weeks	Every 2 weeks	Financial estimates (excluding RSA)
Lanadelumab DPMQ		$	
Doses per year	13	26	20.15
Cost per patient per year [a]	$	$	$

Source: Calculated during evaluation
DPMQ = dispensed price per maximum quantity; RSA = risk sharing agreement
[a] Includes patient co-payments

6.34 The PBAC noted the cost per year is substantially higher with two-weekly dosing versus four-weekly dosing. The PBAC recalled that the lanadelumab RSA was intended to: (a) account for patients receiving the two-weekly dosing regimen; (b) manage the risk of use in cost-ineffective populations; and (c) achieve cost-effectiveness for the listing (paragraph 6.53, lanadelumab PSD, July 2021 PBAC meeting). Further, the PBAC recalled that, in the economic model, the ICER (for patients who would otherwise be treated with standard of care) was based on the assumption that the cost of lanadelumab would be capped at 13 doses per patient per year (i.e. four-weekly dosing), and that the ESC had considered that all expenditure resulting from more frequent dosing would need to be rebated at % to maintain this level of cost-effectiveness (paragraph 6.53, lanadelumab Minutes, July 2021 PBAC meeting).

Estimated PBS usage & financial implications

6.35 This submission was not considered by DUSC.

6.36 The submission presented an epidemiological approach to estimate the PBS use and financial implications. The estimates for the prevalent population were based on DUSC data for the number of patients aged 2-11 years using icatibant. The key inputs for the estimates are shown in Table 7.

Table 7: Key inputs for financial estimates

Parameter	Value applied and source	Evaluation comment
Patients aged 2-11 years treated with icatibant	DUSC data Year: 2021 — Number of patients: 15 Year: 2022 — Number of patients: 15 Year: 2023 — Number of patients: 13	The evaluation considered this may be an underestimate for population requested, as based on trial data – 6/21 in the SPRING trial were NOT receiving icatibant or C1-INH esterase inhibitor within 28 days of entry. The submission also claimed that the icatibant usage data were not reliable. However, the PBAC considered that the submission had likely overestimated the eligible population as a more stringent restriction was recommended.
Uptake rate	Submission estimate based on number of patients on icatibant n=15 Year 1: [redacted]% — [redacted]1 Year 2: [redacted]% — [redacted]1 Year 3: [redacted]% — [redacted]1 Year 4: [redacted]% — [redacted]1 Year 5: [redacted]% — [redacted]1 Year 6: [redacted]% — [redacted]1	The evaluation considered this may be an under or overestimate (based on the submission's proposed restriction). However, the PBAC considered that uptake would likely be high in the context of the restriction recommended, and thus the uptake may have been underestimated.
Compliance rate (doses used in practice in the trial)	Assumes full compliance with lanadelumab 20.15 injections per year, calculated from Maurer (2023)	The evaluation considered that the reference may be incorrect, and calculated that the SPRING CSR Table 11 p91 results in the mean dose over the trial as 22.14 doses. See Table 8 for details.
Grandfathered patients	Submission states 2 patients are currently receiving lanadelumab	Does not appear to add these to the total numbers, however this is likely appropriate as these patients would likely be included in the epidemiological approach used.
Dose/duration	150 mg Q2 or Q4 weekly indefinitely (see compliance rate row above)	Consistent with trial and TGA indication
Offsets for comparator/ subsequent therapies	Not included	Appropriate. While there may be potential offsets for reduced use of C1-INH, this was likely to be minimal (particularly given the criteria for access to C1-INH requires a patient to have experienced at least 8 attacks per month). Further, the submission stated that C1-INH utilisation data in paediatric patients were not available.
MBS item	Not included	Appropriate

Source: Tables 41 and 42 and associated text, pp 59-60 of the submission
The redacted values correspond to the following ranges:
1 < 500

6.37 The evaluation noted that the estimated number of patients aged 2-11 may not account for the full extent of usage under the submission's proposed listing, as when patients reach 12 years of age they will be eligible to continue treatment, despite never having met the criteria for treatment initiation in patients aged ≥12 years. The PSCR claimed that patients who experience HAE attacks prior to 12 years of age would be likely to experience severe disease in adolescence, and therefore qualify under the

treatment initiation criteria for ≥12 years (paragraph 3.6). However, the ESC considered the available data do not provide sufficient evidence to support the sponsor's proposed reduction in baseline attack rate criteria (paragraph 6.27).

6.38 The submission estimated that up to 75% of patients currently treated with icatibant would use lanadelumab, based on the submission's proposed minimum baseline attack rate. The submission also estimated that the expected number of lanadelumab injections per year would be 20.15, based on calculations derived from Figure 2 in Maurer et al. 2024.[12] The calculation was based on the number of patients using the prescribed dose for each period in the SPRING study (which required a minimum baseline attack rate of 2 attacks in 6 months), allowing for patients who discontinued and assuming full compliance. However, the evaluation calculated that the average number of doses used in the SPRING study was 22.1, as summarised in Table 8. The PBAC agreed with the evaluation that the average number of doses should be based on the trial data.

Table 8: Doses received during SPRING study, overall treatment period

	Patients aged 2-6 allocated to 150 mg Q4W	Patients aged 6-11 allocated to 150 mg Q2W
Number of patients (n, %)	4 (19%)	17 (81%)
Mean number of doses (SD)	12.5 (7.55)	24.4 (3.12)
Median (range)	14.0 (2, 20)	27.0 (19, 27)
Weighted average (using the mean)	22.1	

Source: constructed from Table 14.3.7.3, p 5952 and p5954 of the CSR.
Q2W = every 2 weeks; Q4W = every 4 weeks.

6.39 For the submission's requested baseline attack rate of at least 1 in 3 months, the total cost to the PBS/RPBS of listing lanadelumab was estimated to be $0 to < $10 million in Year 6, and a total of $10 million to < $20 million in the first 6 years of listing (Table 9).

Table 9: Estimated use and financial implications (effective price)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients treated	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Number of scripts dispensed[a]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Estimated financial implications of lanadelumab						
Cost to PBS/RPBS less copayments[b] ($)	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]

Source: Table 44, p62 of the submission.
[a] Assuming 20.15 injections per year as estimated by the submission.
[b] Recalculated by the evaluation using the lanadelumab effective price
The redacted values correspond to the following ranges:
1 < 500
2 $0 to < $10 million

[12] Maurer M et al. Lanadelumab in Patients 2 to Less Than 12 Years Old With Hereditary Angioedema: Results From the Phase 3 SPRING Study. *J ALLERGY CLIN IMMUNOL PRACT* 2024; 12(1):201-11.

Financial Management – Risk Sharing Arrangements

6.40 The submission proposed that the use of lanadelumab in the new paediatric population will be incorporated into the existing RSA and subsidisation cap and should therefore result in no additional cost to the Commonwealth.

For more detail on PBAC's view, see section 7 PBAC outcome.

7 PBAC Outcome

7.1 The PBAC recommended the listing of lanadelumab for the preventative treatment of hereditary angioedema (HAE) Types 1 or 2 in patients aged less than 12 years. The PBAC was satisfied that lanadelumab provides, for some patients, a substantial clinical benefit in terms of a reduction in HAE attack frequency versus the comparator, ODT. The PBAC noted that an economic model for the <12 yrs population was not provided, but considered that the model used to support listing in the ≥12 yrs population could be used to support listing in the expanded population.

7.2 The PBAC accepted the clinical need for long term prophylaxis options in patients under the age of 12 years who suffer from frequent HAE attacks.

7.3 The PBAC supported the submission's requested restriction with the exception of the requested threshold of one attack in the preceding 3 months for the 2-11 years population (amended to 2 attacks in the preceding 6 months in the PSCR). The PBAC considered that the HAE attack rate that currently applies to patients ≥12 years (≥12 attacks in the preceding six months) should also apply to patients <12 years. The PBAC considered that the requested lower attack rate could not be supported in terms of extending the economic evaluation previously applied to the ≥12 years population to patients <12 years (see paragraph 7.7 below). The PBAC considered that the 150 mg presentation should be listed age agnostically, with a flow on change to the existing restriction for the 300 mg/2 mL strength to also make that listing age agnostic.

7.4 The PBAC accepted the submission's nominated comparator, ODT with either icatibant or intravenous C1-INH, noting it had been accepted in the PBAC's previous considerations of the ≥12 yr population.

7.5 The PBAC noted the limited data available in the <12 year old HAE population from one small, single-arm trial (the SPRING trial). The PBAC considered that the claim of superior comparative effectiveness of lanadelumab compared to ODT was reasonable, noting that that while the magnitude of benefit was unclear, the available data in patients <12 yrs suggested that lanadelumab has superior efficacy in terms of preventing HAE attacks compared with the number of attacks in the baseline observation period (used as a proxy for ODT with icatibant or C1-INH). Further, the PBAC considered that as there is no mechanistic reason to assume that lanadelumab would differ in efficacy between age groups, the previous data (from patients aged ≥12 years) would support extending the existing listing to patients aged <12 years. However, the PBAC considered that the submission's proposed restriction (with a

lower baseline attack rate than the existing population) was not adequately supported by the single-arm trial data. The PBAC acknowledged that it is unlikely that new clinical data will become available, given the rarity of the disease particularly in this age group.

7.6 The PBAC considered that the claim of inferior comparative safety of lanadelumab compared to ODT was reasonable, noting data limitations associated with the small population. The PBAC noted that it accepted a conclusion of inferior comparative safety for lanadelumab for the >12 years population (paragraph 7.10, lanadelumab PSD, July 2020).

7.7 The PBAC considered that it would be appropriate to expand the existing lanadelumab listing to include children <12 years based on the economic evaluation previously considered for the ≥12 years population. However, the PBAC considered that this model would not be reliable for decision-making if the restriction were to be based on a lower baseline attack rate for the 2-11 years population, given the the sensitivity of the ICER to baseline attack frequency (paragraph 6.7, lanadelumab PSD, July 2021). The PBAC advised that a new submission including an economic model for the 2-11 years population would be required to amend the restriction to require a lower baseline attack rate.

7.8 The PBAC considered that the financial estimates were uncertain because the financial estimates were based on the submission's proposed restriction, which was broader than the restriction recommended in terms of baseline HAE attack frequency. In the context of the PBAC-recommended restriction (≥12 HAE attacks within 6 months with age agnostic listings), the PBAC considered that the submission may have: overestimated the eligible population (as a more stringent restriction was recommended); but underestimated the uptake rate (as the restriction would reflect a population with a higher clinical need).

7.9 The PBAC noted that the submission proposed a grandfather restriction. The PBAC considered that the grandfather provision should allow for patients on the current access program to move onto PBS supply. The PBAC advised that this should only be in effect for 12 months.

7.10 The PBAC recommended that lanadelumab in patients <12 years should be included under the existing RSA for lanadelumab in patients ≥12 years with no increase in expenditure caps, as proposed by the submission.

7.11 The PBAC noted that the submission estimated an average of 20 lanadelumab injections per year in the new population. The PBAC recalled that one of the reasons for the lanadelumab RSA was to account for patients receiving the two-weekly dosing regimen given the economic model was based on the assumption that the cost of lanadelumab would be capped at 13 doses per patient per year i.e. four-weekly dosing (refer to paragraph 6.34). The PBAC advised that given there is substantial utilisation of two-weekly dosing (or any dosing that is more frequent than four-weekly) in clinical practice, it would be preferable to achieve cost-effectiveness via the unit price across the total population using lanadelumab, rather than relying on the RSA.

7.12 The PBAC found that the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were not met. Specifically, the PBAC found that in the circumstances of its recommendation for lanadelumab:

a) The treatment is expected to provide a clinically relevant improvement in efficacy over standard of care, but the magnitude of benefit is uncertain.

b) The treatment is not expected to address a high and urgent unmet clinical need because there are alternative treatment options for HAE in patients <12 years (ODT).

c) It was not necessary to make a finding in relation to whether it would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A because one or more of the preceding tests had failed.

7.13 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:
Recommended

8 Recommended listing

8.1 Add new item:

Initial treatment – New patient
Restriction Summary New/ ToC: New

MEDICINAL PRODUCT medicinal product pack	**PBS item code**	**Max. qty packs**	**Max. qty units**	**№.of Rpts**	**Available brands**
LANADELUMAB					
lanadelumab 150 mg/1 mL injection, 1 mL syringe	NEW MP	1	1	5	TAKHZYRO® TAKEDA Australia Pty Ltd

Concept ID	**Category / Program:** ☒ GENERAL - General Schedule (Code GE)
	Prescriber type: ☒Medical Practitioners
	Restriction type: ☒Authority Required (FULL assessment) in writing only via post/HPOS upload
	Administrative advice: No increase in the maximum number of repeats may be authorised.
	Administrative advice: Special Pricing Arrangements apply.
	Indication: Chronic treatment of hereditary angioedema Types 1 or 2
	Treatment Phase: Initial 1: New patient (commencing with no previous treatment with C1-INH for routine prophylaxis)
	Clinical criteria:
	Patient must have experienced at least 12 treated acute attacks of hereditary angioedema within the 6 month period prior to commencing treatment with this drug
	AND

	Clinical criteria:
	Patient must not have been receiving a C1-esterase inhibitor through the National Blood Authority as routine prophylaxis for hereditary angioedema at the time of application
	AND
	Clinical criteria:
	The treatment must not be used in combination with a C1-esterase inhibitor concentrate
	AND
	Treatment criteria:
	Must be treated by a clinical immunologist or a specialist allergist
	Prescribing instructions: For the purposes of administering this restriction, acute attacks of hereditary angioedema are those of a severity necessitating immediate medical intervention with either (i) icatibant, or (ii) C1-esterase inhibitor concentrate.
	Prescribing instructions: The baseline measurement of the number of treated acute attacks of hereditary angioedema within the 6 months prior to initiating treatment must be provided at the time of submitting this application
	Administrative advice: *Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).* *Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au* *Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos* *Or mailed to:* *Services Australia* *Complex Drugs* *Reply Paid 9826* *HOBART TAS 7001*

Initial treatment – New patient coming from NBA-funded C1-INH
Restriction Summary New/ ToC: New

Concept ID – for Dept. use	**Category / Program:** GENERAL – General Schedule (Code GE)
	Prescriber type: ☒ Medical Practitioners
	Restriction type: ☒ Authority Required (FULL assessment) in writing only via post/HPOS upload
	Administrative advice: No increase in the maximum number of repeats may be authorised.
	Administrative advice: Special Pricing Arrangements apply.
	Indication: Chronic treatment of hereditary angioedema Types 1 or 2
	Treatment Phase: Initial 2: New patient (commencing from National Blood Authority-funded C1-INH)
	Clinical criteria:
	Patient must have been receiving a C1-esterase inhibitor through the National Blood Authority as routine prophylaxis for hereditary angioedema immediately prior to receiving lanadelumab
	AND
	Clinical criteria:
	The treatment must not be used in combination with a C1-esterase inhibitor concentrate
	AND
	Treatment criteria:
	Must be treated by a clinical immunologist or a specialist allergist
	Administrative advice: *Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).*

	Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au *Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos* *Or mailed to:* *Services Australia* *Complex Drugs* *Reply Paid 9826* *HOBART TAS 7001*

Initial treatment – New patient (Grandfather provision)
Restriction Summary New/ ToC: New

Concept ID – for Dept. use	**Category / Program:** GENERAL – General Schedule (Code GE)
	Prescriber type: ☒ Medical Practitioners
	Restriction type: ☒ Authority Required (FULL assessment) in writing only via post/HPOS upload
	Administrative advice: No increase in the maximum number of repeats may be authorised.
	Administrative advice: Special Pricing Arrangements apply.
	Indication: Chronic treatment of hereditary angioedema Types 1 or 2
	Treatment Phase: Transitioning from non-PBS to PBS-subsidised treatment – Grandfather arrangements
	Clinical criteria:
	Patient must have previously received non-PBS subsidised treatment with this drug for this PBS indication prior to *[PBS listing date]*;
	AND
	Clinical criteria:
	The treatment must not be used in combination with a C1-esterase inhibitor concentrate
	AND
	Treatment criteria:
	Must be treated by a clinical immunologist or a specialist allergist
	Prescribing instructions: For the purposes of administering this restriction, acute attacks of hereditary angioedema are those of a severity necessitating immediate medical intervention with either (i) icatibant, or (ii) C1-esterase inhibitor concentrate.
	Administrative advice: This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria.
	Administrative advice: Patients may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a 'Grandfather' patient must qualify under the 'Continuing treatment' criteria.
	Administrative advice: *Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).* *Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au* *Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos* *Or mailed to:* *Services Australia* *Complex Drugs* *Reply Paid 9826* *HOBART TAS 7001*

Continuing treatment

Restriction Summary New/ ToC: New

Concept ID – for Dept. use	**Category / Program:** GENERAL – General Schedule (Code GE)
	Prescriber type: ☒ Medical Practitioners
	Restriction type: ☒ Authority Required (immediate assessment) telephone/online
	Administrative advice: No increase in the maximum number of repeats may be authorised.
	Administrative advice: Special Pricing Arrangements apply.
	Indication: Chronic treatment of hereditary angioedema Types 1 or 2
	Treatment Phase: Continuing preventative treatment
	Clinical criteria:
	Patient must have previously received PBS-subsidised treatment with this drug for this condition
	AND
	Clinical criteria:
	Patient must have demonstrated or sustained an adequate response to PBS-subsidised treatment with this drug for this condition
	AND
	Clinical criteria:
	The treatment must not be PBS subsidised in combination with a C1-esterase inhibitor concentrate
	AND
	Treatment criteria:
	Must be treated by a specialist allergist or clinical immunologist, or in consultation with a specialist allergist or clinical immunologist
	Prescribing instructions: Patients who have successfully transitioned to a lower dosing frequency should be reviewed every 6 months to ensure they continue to demonstrate a sustained response
	Prescribing instructions: For the purposes of administering this restriction, an adequate response is a reduction of the baseline number of acute attacks of hereditary angioedema of a severity necessitating immediate medical intervention with either (i) icatibant, or (ii) C1-esterase inhibitor concentrate. The details of the reduction must be documented in the patient's medical records for auditing purposes
	Administrative advice: *Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday)*

The PBAC recommended a flow on change to the existing restriction for lanadelumab 300 mg/2 mL in hereditary angioedema Types 1 or 2 (PBS item code: 12790E):

- **Update to the population criteria to make the listing age agnostic.**

Population criteria:
~~• Patient must be aged 12 years or older.~~

These restrictions may be subject to further review. Should there be any changes made to the restriction the sponsor will be informed.

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in

relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

10 Sponsor's Comment

The sponsor had no comment.