7.02 LANADELUMAB, Solution for subcutaneous injection 300 mg in 2 mL, Takhzyro®, Takeda Pharmaceuticals Australia Pty Ltd

1 Purpose of resubmission

1.1 The standard re-entry submission requested a Section 85, Authority Required listing for lanadelumab as routine prophylaxis of recurrent attacks of hereditary angioedema (HAE).

1.2 Listing was requested on the basis of a cost-utility analysis of lanadelumab compared with standard of care (SOC) in patients with HAE. The key components of the overall clinical claim addressed by the resubmission are summarised below.

Table 1: Key components of the clinical issue addressed by the resubmission

Component	Description
Population	Patients who experienced at least 12 treated acute HAE attacks within a 6-month period[a]
Intervention	Lanadelumab subcutaneous injection
Comparator	SOC for HAE, which comprises use of ODT (icatibant and/or IV C1-INH)[b]
Outcomes	Outcomes used in the economic evaluation: HAE attack rate HAE attack rate requiring acute treatment
Clinical claim	The PBAC previously considered that the claim of superior effectiveness and inferior safety versus SOC was reasonable, noting that, based on the evidence available, lanadelumab appears to be well tolerated (Para 6.27 and 7.10, July 2020 PSD).

Source: Compiled during the evaluation based on information provided in Sections 1-3 of the resubmission.
C1-INH = C1 esterase inhibitor; HAE = hereditary angioedema; IV = intravenous; ODT = on-demand treatment; PSD = Public Summary Document; SOC = standard of care.
Note: Underlined text indicates changes compared with the resubmission considered in July 2020:
[a] The population in the July 2020 resubmission was patients who experienced at least 12 treated acute HAE attacks within a 6-month period and are intolerant or insufficiently protected by oral routine prophylaxis.
[b] The comparator in the July 2020 resubmission was SOC for HAE, comprising of ODT (icatibant or IV C1-INH) with oral routine prophylaxis.

2 Background

Registration status

2.1 Lanadelumab was granted orphan drug designation by the TGA on 21 February 2018, and was listed on the Australian Register of Therapeutic Goods on 30 January 2019 for routine prevention of recurrent attacks of HAE (C1 esterase inhibitor (C1-INH) deficiency or dysfunction) in patients aged 12 years and older.

Previous PBAC consideration

2.2 The key matters of concern raised by the previous PBAC consideration are summarised below.

Table 2: Summary of key matters of concern

Component	Matter of concern	How the resubmission addresses it
Population	The following need to be determined: • the appropriate baseline number and type of HAE attacks for lanadelumab eligibility to ensure use is targeted to a sufficiently high risk population, and • continuation criteria that ensure that ongoing use is targeted to patients deriving appropriate clinical benefit. (Para 7.3, 7.4 and 7.18, July 2020 PSD).	Not adequately addressed. The number of baseline HAE attacks for lanadelumab eligibility remained unchanged; no justification was provided for the proposed threshold number of attacks for lanadelumab eligibility. Qualifying HAE attacks were defined as those of a severity necessitating medical intervention. It was not clear whether the use of ODT, which is often self-administered, represented 'medical intervention'. The continuation criteria has not been refined; the definition of an adequate response has been removed from the proposed restriction and replaced by "as judged by the treating clinician."
Clinical evidence	As routine prophylaxis was not permitted in the HELP trial, the treatment effect in Australian clinical practice may be lower than observed in the trial (Para 7.8, July 2020 PSD).	Addressed. As danazol is no longer available on the PBS, the limited use of oral prophylaxis in the trial is consistent with current clinical practice. The requirement for initiating patients to be intolerant of or insufficiently protected by oral routine prophylaxis was removed from the restriction.
Economic evaluation	The key issues were the baseline attack rate applied in the model, uncertainty around the dosage regimen that would be likely used in clinical practice, and the likely optimistic between-attack utilities that were applied (Para 7.13, July 2020 PSD).	See below
	The ICER was highly sensitive to the baseline HAE attack rate. The distribution of baseline frequency of HAE attacks applied in the economic model was highly uncertain given it was based on only 11 patients (Para 6.34 and 7.11, July 2020 PSD).	Addressed. The distribution of baseline HAE attack rates was based on PBS data for icatibant from 2016 to 2019. This included data for at least 20-30 patients each year.
	There was a large difference between the number of attacks required for PBS eligibility and the point at which lanadelumab would likely become cost-effective (Para 7.11, July 2020 PSD)	Not addressed
	As there was no demonstrated difference in efficacy between lanadelumab 300 mg Q2W and the 300 mg Q4W regimen, it may be appropriate to cap the cost per patient at no more than that for the 300 mg Q4W regimen (Para 7.9, July 2020 PSD)	Addressed. The economic evaluation applied a fixed cost per patient, assuming 13 injections of lanadelumab per year (300 mg Q4W). However, this was not entirely consistent with the RSA proposed in the resubmission, as it failed to apply [redacted]% of the cost for any usage above this dosage (see below).
	The approach to estimating between-attack utilities likely overestimated the utility decrement associated with each incremental increase in the number of treated attacks (Para 6.45, July 2020 PSD).	Not addressed.
Financial estimates	The financial estimates may have been overestimated as the submission effectively applied prevalence estimates as incidence estimates (Para 7.14, July 2020 PSD).	Prevalence data have been used appropriately. The estimated cost to the PBS/RPBS remains highly uncertain.

Component	Matter of concern	How the resubmission addresses it
Risk share arrangement	There is a substantial risk of use of lanadelumab outside the restriction in patients experiencing fewer HAE attacks than permitted under the restriction (Para 7.15, July 2020 PSD). An updated RSA proposal would be required, to manage the risks of use in cost-ineffective populations, and the uncertainty in the dosage regimens. A [redacted]% rebate should apply for any usage above the total cap (Para 7.16-7.18 July 2020 PBAC PSD)	Not adequately addressed. While an updated RSA was provided, it did not include a [redacted]% rebate above the total cap. A [redacted]% rebate was proposed.

Source: Lanadelumab PSD, July 2020 PBAC meeting; Lanadelumab PBAC PSD, July 2020 PBAC meeting; Sections 1, 3 and 4 of the resubmission.
HAE = hereditary angioedema; ICER = incremental cost-effectiveness ratio; ODT = on-demand treatment; PSD = Public Summary Document; Q2W = every 2 weeks; Q4W = every 4 weeks; RSA = risk sharing arrangement.

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

3 Requested listing

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Price for Max. Qty [a]	Proprietary Name and Manufacturer
LANADELUMAB 300 mg/2 mL solution, pre-filled syringe	2	5	Published price $37,202.53[b] *($37,041.36)* Effective price $[redacted] *($[redacted])*	Takhzyro®, Takeda Australia Pty Ltd

Source: Table 2 of the resubmission.
[a] Published AEMP: $18,440.10 for 1 x 300 mg syringe; effective AEMP: $[redacted] for 1 x 300 mg syringe.
[b] In calculating the dispensed price for maximum quantity (2 syringes), the resubmission appears to have doubled the dispensed price for one syringe, rather than adding the mark-ups and fees ($161.16) to the EMP for 2 syringes. The corrected dispensed price for maximum quantity is provided in italics.

Category / Program:	GENERAL – General Schedule (S85) (Code GE)
PBS Indication:	Hereditary angioedema Type 1 or 2
Treatment phase:	Initial 1: New patient (no prior use of National Blood Authority-funded C1-INH)
Restriction:	☒Authority Required – immediate/real time assessment by Services Australia (telephone/online)
Treatment criteria:	Must be treated by at least one of a: clinical immunologist / specialist allergist.
Clinical criteria:	Patient must have experienced at least 12 treated acute attacks of hereditary angioedema within the 6 months prior to commencing treatment with this drug, AND The treatment must not be PBS-subsidised in combination with a C1-esterase inhibitor concentrate.
Prescriber Instructions:	For the purposes of administering this restriction, acute attacks of hereditary angioedema are those of a severity necessitating immediate medical intervention. The baseline number of treated attacks of hereditary angioedema within the 6 months prior to initiating treatment must be documented in the patient's medical records for auditing purposes.

Category / Program:	GENERAL – General Schedule (S85) (Code GE)
PBS Indication:	Hereditary angioedema Type 1 or 2
Treatment phase:	Initial 2: New patient (prior use of National Blood Authority-funded C1-INH)

Restriction:	☒Authority Required – immediate/real time assessment by Services Australia (telephone/online)
Treatment criteria:	Must be treated by a specialist allergist or clinical immunologist, or in consultation with a specialist allergist or clinical immunologist.
Clinical criteria:	Patient must be currently receiving C1-esterase inhibitor through the National Blood Authority as routine prophylaxis for HAE, AND The treatment must not be PBS-subsidised in combination with a C1-esterase inhibitor concentrate.
Prescriber Instructions:	For the purposes of administering this restriction, acute attacks of hereditary angioedema are those of a severity necessitating immediate medical intervention. The baseline number of treated attacks of hereditary angioedema within the 6 months prior to initiating treatment must be documented in the patient's medical records for auditing purposes.

Category / Program:	GENERAL – General Schedule (S85) (Code GE)
PBS Indication:	Hereditary angioedema Type 1 or 2
Treatment phase:	Initial 3: New patient (patient initiated on non-PBS subsidised treatment)
Restriction:	☒Authority Required – immediate/real time assessment by Services Australia (telephone/online)
Treatment criteria:	Must be treated by at least one of a: clinical immunologist / specialist allergist.
Clinical criteria:	Patient must have previously received non-PBS subsidised treatment with this drug as routine prophylaxis for HAE prior to [date to be determined], AND Patient must have experienced at least 12 treated acute attacks of HAE within the 6 months prior to commencement of treatment, AND The treatment must not be PBS-subsidised in combination with a C1-esterase inhibitor concentrate.
Prescriber Instructions:	For the purposes of administering this restriction, acute attacks of hereditary angioedema are those of a severity necessitating immediate medical intervention. The baseline number of treated attacks of hereditary angioedema within the 6 months prior to initiating treatment must be documented in the patient's medical records for auditing purposes.

Category / Program:	GENERAL – General Schedule (S85) (Code GE)
PBS Indication:	Hereditary angioedema Type 1 or 2
Treatment phase:	Continuing preventative treatment
Restriction:	☒Authority Required – immediate/real time assessment by Services Australia (telephone/online)
Treatment criteria:	Must be treated by a specialist allergist or clinical immunologist, or in consultation with a specialist allergist or clinical immunologist.
Clinical criteria:	Patient must have previously received PBS-subsidised treatment for this condition, AND Patient must have demonstrated or sustained an adequate response to PBS-subsidised treatment with this drug for this condition, as judged by the treating clinician, AND This medicine is not PBS-subsidised for use in combination with C1-esterase inhibitor concentrate.

3.1 The pre-PBAC response requested that, if listed, the Initial treatment restrictions be Authority Required – non-immediate assessment (i.e. written) rather than immediate/real time assessment. The pre-PBAC response stated that this would help record initiation information and could be helpful to inform future DUSC reviews. The PBAC considered that Authority Required – non-immediate assessment listings were appropriate for the Initial treatment restrictions.

3.2 The pre-PBAC response also requested that the restrictions include a population criteria requiring patients to be 12 years of age or older, as the TGA approved Product

Information states that treatment in children aged less than 12 years is not recommended. The PBAC considered that this addition was appropriate.

3.3 Further, the pre-PBAC response suggested reducing the maximum quantity per prescription to one syringe per month (effective approved ex-manufacturer price (AEMP) = $[redacted]; effective dispensed price for maximum quantity (DPMQ) = $[redacted]). The PBAC considered this was appropriate.

3.4 A comparison between the eligibility (Initial treatment 1 restriction) and continuation criteria presented above and that proposed in the July 2020 resubmission is summarised below. The Initial 2 restriction was essentially unchanged from the previous resubmission, while the Initial 3 restriction was similar to the Initial 1 restriction, other than the requirement that the patient must have previously received non-PBS subsidised treatment with lanadelumab as routine prophylaxis for HAE.

Table 3: Comparison of eligibility and continuation criteria across the resubmissions

Criteria	Resubmission considered in July 2020	Current resubmission
Eligibility – Initial 1	Patient must have experienced at least 12 treated acute attacks of HAE within a period of 6 months prior to commencement of treatment, and Patient must be intolerant or insufficiently protected by oral routine prophylaxis	Patient must have experienced at least 12 treated acute attacks of HAE within a period of 6 months prior to commencement of treatment. For the purposes of administering this restriction, acute attacks of HAE are those of a severity necessitating medical intervention.
Continuation	Patient must have demonstrated or maintained a treatment response to treatment with this drug. For patients initiating under the Initial – 1 restriction, treatment response is defined as a reduction of 50% from baseline in the number of treated acute attacks of HAE per month compared to baseline.	Patient must have demonstrated or sustained an adequate response to PBS-subsidised treatment with this drug for this condition, as judged by the treating clinician. No definition of an adequate response was proposed in the restriction.

Source: Table 3, p10 of the resubmission; Lanadelumab PSD, July 2020 PBAC meeting.
HAE = hereditary angioedema.

3.5 The PBAC previously had the following concerns regarding the eligibility and continuation criteria proposed in the July 2020 resubmission:

- The PBAC considered that consultation with clinicians who are experienced at managing HAE would be required to determine the appropriate baseline number and type of attacks for lanadelumab eligibility to ensure use is targeted to a sufficiently high risk population in light of the high cost per patient of the drug (paragraph 7.3, lanadelumab, Public Summary Document (PSD), July 2020).
- The PBAC considered there were several issues with the proposed continuation criteria including that it does not account for attack severity and may be difficult to reliably assess. The PBAC considered that the rationale for the proposed continuation criteria was unclear and that further consultation with clinicians who are experienced at managing HAE would be required to ensure ongoing use is targeted to patients deriving appropriate clinical benefit from lanadelumab (paragraph 7.4, lanadelumab PSD, July 2020).

3.6 In October 2020, a stakeholder meeting was held to receive clinical and patient perspectives on the issues outlined above. The participants advised that basing eligibility for subsidised access to lanadelumab on attack frequency alone would not adequately capture the group of patients most likely to benefit. The participants expressed a preference for the restriction to take into account a range of factors, such as access to medical care, burden of attacks, number of attacks, quality of life, mental health impacts, and work or productivity impairment. The clinical experts also emphasised the need for the restriction to be practical for use in clinical practice. In terms of the continuation criteria or a stopping rule, participants discussed that it would be difficult to cease lanadelumab once it has been initiated (except in patients deriving limited clinical benefit), reiterating the value of prophylaxis on quality of life (Lanadelumab stakeholder meeting summary, October 2020).

3.7 The resubmission stated that the participants at the stakeholder meeting raised a concern that the restriction as written did not account for patients who experienced fewer attacks but had a high burden of disease. A consistent method for determining this burden was not identified; however, the angioedema quality of life questionnaire (AE-QoL) was suggested as a potential solution. The resubmission presented an alternative restriction for consideration but stated that the sponsor was not proposing to introduce these criteria at this time, but that it would monitor any ongoing requests for access for people who do not qualify under the proposed restriction in order to determine the key characteristics and benefits of treatment for those patients.

3.8 As danazol is no longer listed on the PBS, the exclusion of the criterion that the patient must be intolerant of, or insufficiently protected by, oral routine prophylaxis was reasonable. This was also consistent with the key clinical evidence presented in the previous resubmission (HELP trial), in which only 5.6% of patients were receiving oral prophylaxis with danazol.

3.9 In July 2020, the PBAC raised concerns regarding the appropriate baseline number and type of attacks for lanadelumab eligibility. However, the:

- number of baseline HAE attacks for lanadelumab eligibility remained unchanged in the July 2021 resubmission; no justification was provided for the proposed threshold number of attacks. In contrast to '≥12 treated acute attacks of HAE within a period of 6 months' (an average of two attacks per month), the inclusion criteria for the HELP trial specified a baseline rate of greater than or equal to one HAE attack every 4 weeks. The mean number of attacks requiring acute treatment in the placebo arm of HELP was 1.64 per 4 weeks (approximately 21 per year);
- resubmission defined 'acute attacks' as those of a severity necessitating medical intervention. The resubmission did not state whether the use of on-demand

treatment (ODT) (icatibant or intravenous (IV) C1-INH[*]), which is often self-administered, represented 'medical intervention'. If so, it is not clear how this definition differs from 'treated acute HAE attacks', and how this addresses the PBAC's concerns. The ESC considered that an 'acute attack necessitating medical intervention' would be an attack of a severity that required targeted on-demand therapy (i.e. icatibant or C1-INH).

As noted above, the participants of the stakeholder meetings advised that lanadelumab eligibility should not be based on attack frequency alone, and preferred to consider a range of factors and to be practical for use in clinical practice. The Pre-Sub-Committee Response (PSCR) noted that the stakeholder meeting suggested broadening the initial restriction to include non-attack related criteria, but stated that the proposed restriction was intended to capture the majority of patients likely to benefit most from lanadelumab whilst demonstrating reasonable cost-effectiveness. The ESC noted that although a holistic approach to eligibility would be ideal, providing evidence to support this approach would be difficult. The ESC considered that the incorporation of quality of life scores into the initial restrictions would not resolve all the issues raised in the stakeholder meeting and might not necessarily assist with ensuring that patients who would derive the greatest benefit from therapy were targeted.

3.10 The exclusion of the definition of treatment response, and the amended requirement that a patient demonstrate a sustained or adequate response, as judged by the treating clinician, also did not adequately address the PBAC's concern that ongoing use be targeted to patients deriving appropriate clinical benefit from lanadelumab. The resubmission stated that the three clinicians and the patient advocate who attended the stakeholder meeting outlined the intra-patient unpredictability of HAE and the debilitating effect this has on quality of life; the participants discussed that it would be difficult to cease lanadelumab once it has been initiated (except in patients deriving limited clinical benefit). The ESC considered that the inclusion of quality of life scores into the continuing restrictions may not offer additional value to specialist clinician assessment. In addition, the ESC, noting that the proposed continuation criteria was not dissimilar to that for omalizumab for severe chronic spontaneous urticaria, which states "Patient must have demonstrated a response to the most recent PBS-subsidised treatment with this drug for this condition", considered that, with a suitable risk sharing arrangement (RSA) the continuation criteria for this rare genetic disorder, which would be managed by a small group of specialists, was reasonable.

3.11 The resubmission proposed a special pricing arrangement (SPA), with the proposed effective ex-manufacturer price in the current resubmission being the same as that

[*] The subcutaneous preparation of C1-INH (Berinert SC) is only registered on the Australian Register of Therapeutic Goods for the prevention of recurrent HAE attacks.

proposed in the July 2020 resubmission. The pre-PBAC response proposed a revised effective price based on the price of one syringe (see paragraph 3.3).

3.12 The resubmission also proposed a risk sharing arrangement (RSA) to manage the risk of use of lanadelumab in the potentially cost-ineffective population (see below for detail). This was updated in the pre-PBAC response.

3.13 The resubmission requested a grandfather provision to allow patients receiving lanadelumab via an access program to transition to PBS-subsidised treatment. It stated that there are currently 12 patients on the access program.

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

4 Population and disease

4.1 HAE is a rare, autosomal dominant, potentially severely debilitating, and life-threatening condition that manifests as painful, unpredictable, intermittent attacks of subcutaneous or submucosal oedema of the face, upper airways, gastrointestinal tract, limbs and/or genitalia. Attacks recur with unpredictable frequency, intensity and duration, placing a burden on the daily life of patients.

4.2 HAE Types 1 and 2 are caused by mutations in the C1-INH gene. Type 1 is due to deficiency of C1-INH, and Type 2 is due to dysfunction of C1-INH.

4.3 Lanadelumab is a human, monoclonal antibody (IgG1/k-light chain) that inhibits plasma kallikrein with a half-life of 14 days.

4.4 Attack frequency and severity among patients is variable, with most patients experiencing few attacks, which can be managed with ODT. Other patients have multiple attacks per month or per week, necessitating prophylactic treatment. Patients who experience at least 12 treated acute attacks of HAE within a period of 6 months are proposed to be eligible for lanadelumab.

4.5 Currently, patients with the equivalent of eight or more attacks per month can access IV or subcutaneous (SC) C1-INH (Berinert®) as routine prophylaxis, funded through the National Blood Authority (NBA)'s National Product List (NPL)[†].

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

5 Comparator

5.1 The resubmission nominated SOC, consisting of use of ODT with icatibant or IV C1-INH, as the main comparator. As danazol is no longer listed on the PBS, in contrast to the July 2020 resubmission, routine oral prophylaxis was no longer considered a component of SOC.

[†] Under the 'National Blood Agreement', there is joint funding by the Commonwealth and the States and Territories in agreed proportions (https://www.blood.gov.au/national-blood-agreement.

5.2 At the July 2020 PBAC meeting, the PBAC considered that the comparator nominated by the submission, on-demand treatment (with icatibant or IV C1-INH) plus oral routine prophylaxis, was appropriate, particularly in patients who experience fewer than eight HAE attacks per month (paragraph 7.6, lanadelumab PSD, July 2020). As danazol is no longer available, the only oral prophylactic available on the PBS is tranexamic acid. The Australasian Society of Clinical Immunology and Allergy (ASCIA) 2020 HAE Position Paper states that use of tranexamic acid for long term prophylaxis is limited due to its relative lack of efficacy[‡]. Therefore, the exclusion of routine oral prophylaxis as a component of SOC in the nominated comparator was reasonable. Furthermore, in the key trial presented in the previous resubmission (HELP), only 5.6% of patients were receiving oral prophylaxis with danazol. The limited use of oral prophylaxis in the SOC arm of the trial is consistent with nominated comparator.

5.3 In July 2020, the PBAC further considered that, while routine prophylaxis with C1-INH may be an appropriate comparator for patients who experience eight or more attacks per month, this is expected to represent only a small proportion of patients (paragraph 7.6, lanadelumab PSD, July 2020). Routine prophylaxis with either IV or SC C1-INH was still considered an appropriate comparator for this patient population. The resubmission did not present a comparison of lanadelumab and routine prophylaxis with C1-INH in patients who experience eight or more HAE attacks per month.

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

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 (26), and organisations (1) via the Consumer Comments facility on the PBS website. The comments from individuals were supported by HAE Australia and described the debilitating and unpredictable nature of HAE attacks and the significant impact HAE has on quality of life. The comments highlighted the benefits associated with lanadelumab treatment including the ease of administration, efficacy in reducing attacks and the resulting improvements to quality of life.

Clinical trials

6.3 The resubmission did not present any clinical evidence.

6.4 The PBAC previously considered that the claim of superior comparative effectiveness was reasonable but considered there was residual uncertainty in the magnitude of

[‡] ASCIA HAE Working Party. *Hereditary Angioedema (HAE) Position Paper*. 2020.

benefit due to the small patient numbers in the trial and potential applicability issues. It further considered that the claim of inferior comparative safety was reasonable, and that, based on the evidence available, lanadelumab appears to be well tolerated (paragraphs 6.27 and 6.28, lanadelumab PSD, July 2020).

Economic analysis

6.5 The resubmission presented an updated economic evaluation based on the direct randomised trial HELP and implemented a modelled evaluation. The type of economic evaluation presented was a cost-utility analysis. The type of analysis and the structure of the model was unchanged from the resubmission considered in July 2020.

6.6 The economic evaluation only assessed the cost-effectiveness of lanadelumab compared with SOC; it did not present a comparison with the use of C1-INH as routine prophylaxis in patients experiencing eight or more attacks per month. The PSCR stated that this comparison was presented in the original July 2019 submission and was limited due to the interchangeability issues between the trial evidence that exists. A comparison of the estimated average treatment costs per year of lanadelumab and C1-INH predicted that treatment with lanadelumab would be less than half that of C1-INH.

6.7 At its July 2020 meeting, the PBAC noted the following regarding the economic model presented in the previous resubmission:

- The base case of the economic evaluation, which resulted in an incremental cost-effectiveness (ICER) of $45,000 to < $55,000/quality-adjusted life year (QALY), was uncertain and optimistic and that the ICER could plausibly be higher than $955,000 to < $1,055,000/QALY. The PBAC considered that the key issues were the baseline attack rate applied in the model, uncertainty around the dosage regimen that would be likely used in clinical practice, and the likely optimistic between-attack utilities that were applied (paragraph 7.13, lanadelumab PSD, July 2020).
- The ICER was highly sensitive to the baseline HAE attack rate. The PBAC noted there was a large difference between the number of attacks required for PBS eligibility and the point at which lanadelumab would likely become cost-effective. (paragraph 7.11, lanadelumab PSD, July 2020).
- There was a substantial difference in the cost per patient between the 300 mg every four weeks (Q4W) and every two weeks (Q2W) dose ($[redacted] versus $[redacted] per patient per year). The PBAC further considered that, given the difference in cost for the two regimens was not supported by a demonstrated difference in efficacy, it may be appropriate to cap the cost per patient at no more than that for the 300 mg Q4W regimen (paragraph 7.9, lanadelumab PSD, July 2020).
- The model was sensitive to the efficacy estimates and applying the estimate for the Q4W treatment arm (which was assumed to be used in 77% of patients) rather

than the Q2W arm had a moderate impact on the ICER (paragraph 7.13, lanadelumab PSD, July 2020).

6.8 The key changes in the economic model, compared with the model in the previous resubmission, are summarised below.

Table 4: Key differences between the economic models presented in the current resubmission and the July 2020 resubmission

Component	Resubmission considered in July 2020	Current resubmission
Baseline HAE attack frequency	Used a 100% PBS data sample to derive the number of icatibant injections dispensed to initiating patients over 12-months, for patients initiating on icatibant between 1 August 2012 and 31 October 2015. Distribution of HAE attacks in the SOC arm was based on 11 patients who had been dispensed ≥ 24 injections over a 12-month period (4.6% of patients). Mean number of attacks in SOC arm: 55.0 per year.	PBS data for patients dispensed icatibant from 2016 to 2019, presented as the number of patients who were dispensed a given number of icatibant injections in each calendar year. For privacy reasons, where the number of patients dispensed a given number of injections within a given calendar year was not zero but less than 5, it was reported as <5 patients. For the analysis, it was assumed that '<5' was exactly one patient. Between 20 and 31 patients were identified as having been dispensed ≥ 24 injections of icatibant over each calendar year from 2016-2019 (total of 107 patient years). Mean number of attacks in SOC arm: 54.8 per patient year.
Dosage regimen	Distribution of doses: 77.1% lanadelumab 300 mg Q4W 22.9% lanadelumab 300 mg Q2W Weighted average of 15.98 doses per year Average cost of $[redacted]/patient/year	The resubmission applied the cost for the lanadelumab 300 mg Q4W treatment regimen to all patients, i.e. 13 doses per year Average cost of $[redacted]/patient /year This was intended to reflect the RSA proposed in the resubmission (see below for detail).
Cost of icatibant	DPMQ $2,455.87 for 1 syringe	DPMQ $850.66 for 1 syringe [a]

Source: Table 12, p25, and Sections 3.2.1, 3.2.2 and 3.2.3 of the resubmission.

DPMQ = dispensed price for maximum quantity; HAE = hereditary angioedema; Q2W = every 2 weeks; Q4W = every 4 weeks; RSA = risk sharing arrangement; SOC = standard of care.

[a] A generic version of icatibant was listed on the PBS in October 2020.

6.9 The model structure, key inputs and rationale for the current resubmission are summarised below.

Table 5: Key components of the economic evaluation

Component	Description
Treatment	Lanadelumab versus SOC. Dosage was updated compared with the previous resubmission (see Table 4 above)
Population	Patients experiencing ≥ 24 treated attacks over 12 months (i.e. ≥ 12 attacks per 6 months, as per the proposed PBS restriction). Baseline HAE attack frequency was updated compared with the previous resubmission (see Table 4 above)
Type of analysis	Cost-utility analysis. Unchanged from previous resubmission
Time horizon	1 year. Unchanged from previous resubmission.
Outcomes	HAE attacks, quality-adjusted life years. Unchanged from previous resubmission
Health-related quality of life	'Between-attack' utility: <1 attack/28 days 0.88, 1 to <2 attacks/28 days 0.80, ≥2 attacks/28 days 0.64 'In-attack' disutility: Mild attack 0.070, moderate attack 0.369, severe attack 0.486 Unchanged from previous resubmission.
Treatment effect	Lanadelumab 300 mg Q2W arm of HELP. Unchanged from the previous resubmission, despite the cost of treatment being based on lanadelumab 300 mg Q4W and the PBAC previously noting that the model was moderately sensitive to the small difference in efficacy between lanadelumab 300 mg Q4W and Q2W.
Methods used to generate results	Cohort expected value. Unchanged from previous resubmission.

Source: Compiled during the evaluation from information provide in Section 3 of the resubmission and the Excel workbook 'LANA_Resubmission_Minor_HAE_Sec3_CUA'.
HAE = hereditary angioedema; Q2W = every 2 weeks; Q4W = every 4 weeks; SOC = standard of care.

6.10 As in the July 2020 resubmission, the resubmission used the number of icatibant injections dispensed to each patient in each calendar year as a proxy for the number of treated HAE attacks per year. The PBAC previously noted that the number of injections of icatibant dispensed may not be a reliable proxy for the number of treated HAE attacks, as patients may require more than one injection of icatibant per attack, and some patients may have multiple injections on hand in anticipation of attacks (paragraphs 6.34 and 7.12, lanadelumab PSD, July 2020). The resubmission argued that, given the intended patient population is a high attack frequency population, it is unlikely that a unit of icatibant dispensed will not be used to treat an attack. This remains a source of uncertainty.

6.11 The baseline frequency of treated attacks in the proposed PBS population was estimated from a DUSC analysis of PBS data for patients dispensed icatibant from 2012 to 2019. The base case of the economic model used the data from 2016 to 2019. The resubmission noted that C1-INH prophylaxis became available in 2016, and argued that it was appropriate for the underlying data source to reflect a population that has already accounted for the underlying efficacy/effectiveness of C1-INH. Ideally, patients receiving routine prophylaxis with C1-INH should not have been included in this analysis, as they would be eligible for lanadelumab through a separate restriction, regardless of their current HAE attack frequency; however, it was not possible to identify these patients.

6.12 In comparison to the previous resubmission, in which the distribution of baseline HAE attack frequencies in the eligible population was based on 12 months of PBS data for 11 patients, in the current resubmission the distribution was based on 107 patient

years of data, with a mean number of attacks in the eligible population being 54.8 per patient year. This was similar to a mean of 55 attacks per patient per year in the previous resubmission. The ESC noted that, whilst these estimates were reasonable, there was a risk of regression to the mean as the number of attacks in one year does not necessarily predict the number of attacks that would have occurred in the subsequent year, and was likely to overestimate it. Given the strong relationship between the attack rate and the ICER, the ESC considered that this, in combination with the issues outlined paragraph 6.28, resulted in an ICER which was likely underestimated.

6.13 The ESC noted that the use of the number of icatibant injections dispensed per patient within each calendar year, 2016-2019 inclusive, to derive the distribution of the baseline number of attacks per patient per year for the purposes of the economic evaluation, was subject to the following limitations:

- Patients may require more than one injection of icatibant per attack, and some patients may have multiple injections on hand in anticipation of attacks;
- It was not possible to identify patients who were receiving routine prophylaxis with C1-INH;
- In the current clinical setting, where danazol is no longer available, the mean number of attacks per patient per year may be higher than during the period over which the data were collected, where a proportion of patients were likely to have been receiving danazol for routine oral prophylaxis of attacks;
- For privacy reasons, if 1-5 patients were dispensed a specific number of injections within any calendar year, this was reported as < 5 patients. In addition, the precise number of injections for patients receiving ≥ 100 injections over the year was not reported. Therefore, the exact distribution of the number of icatibant injections dispensed per patient was not known. Over the calendar years 2016-2019, 74% of inputs were reported as <5 and were imputed as one patient; and
- Some patients may use on-demand IV C1-INH to treat acute attacks, rather than icatibant (the model assumed that only 65% of acute attacks were treated with icatibant).

6.14 Patients experiencing at least eight acute HAE attacks per month (the equivalent of 96 attacks per year) would be eligible for routine prophylaxis with either IV or SC C1-INH. These patients represented 15% (16/107) of the patient years for patients eligible for lanadelumab (those experiencing ≥ 24 attacks per year), and accounted for 27% (1,596/7,855) of the total number of treated HAE attacks in the eligible population. As discussed above, C1-INH may be a more appropriate comparator than SOC for these patients.

6.15 The lanadelumab Product Information (PI) recommends that patients commence on 300 mg Q2W but that, in patients who are stably attack free on treatment, a dose reduction to 300 mg Q4W may be considered. In both the original submission and the

July 2020 resubmission, in the economic evaluation, the cost of lanadelumab was based on the assumption that 22.9% of patients would receive lanadelumab 300 mg Q2W and 77.1% would receive the lower dose of 300 mg Q4W. The PBAC previously considered that, given the difference in cost for the two regimens was not supported by a demonstrated difference in efficacy, it may be appropriate to cap the cost per patient at no more than that for the 300 mg Q4W regimen (paragraph 7.9, lanadelumab, PSD, July 2020 PBAC meeting).

6.16 The resubmission stated that, based the PBAC advice, for the purposes of calculating annual treatment costs, the model assumes that all patients will be treated with the lanadelumab 300 mg Q4W regimen (i.e. 13 syringes per annum), at an effective dispensed price of $[redacted] per patient per year. The resubmission acknowledged that this approach did not alter the uncertainty around the dosage regimen that would be used in clinical practice, but that the resubmission was proposing a cap on expenditure aligned with this annual cost per patient, meaning that any utilisation above the level upon which the cost-effectiveness of lanadelumab was assessed would be heavily discounted. Whether the total cost of lanadelumab reaches the annual subsidisation cap would depend on the accuracy of the resubmission's estimation of the number of patients likely to be treated each year. If the number of patients per year is overestimated, the annual cost per patient for lanadelumab in clinical practice may exceed the annual cost per patient applied in the model. Furthermore, the RSA only proposed a rebate of [redacted]% for utilisation of lanadelumab above the proposed caps. Therefore, any utilisation above 13 injections per patient would need to be costed at [redacted]% of the proposed price. The revised RSA in the pre-PBAC response proposed a rebate of [redacted]% for any utilisation above 13 injections per patient per year.

6.17 The treatment effect relative to SOC (relative risk reduction (RRR) 0.873) from the lanadelumab 300 mg Q2W arm was applied to the baseline number of attacks to estimate the number of attacks in the lanadelumab arm of the model. Given the uncertainty around the dosage regimen that would be likely used in clinical practice, it would have been more conservative to use the outcome for the lanadelumab 300 mg Q4W arm of the trial (RRR 0.742). Applying the RRR from the lanadelumab 300 mg Q4W arm of HELP increased the ICER to $155,000 to < $255,000/QALY. The PSCR acknowledged that applying the efficacy from the Q4W arm of the HELP study would be more conservative but stated that this did not represent what would happen in clinical practice. The ESC considered that applying the effectiveness of the Q2W arm of the HELP study to 100% of the modelled patients was not justified. The ESC suggested that it would have been more appropriate to apply a weighted treatment effect, based on the likely distribution of the dosage regimens. A weighted efficacy (RRR = 0.77176) was applied in a revised economic model presented in the pre-PBAC response (see paragraph 6.29).

6.18 The ESC noted that both the between-attack utilities and the in-attack disutilities applied in the economic model remained unchanged from the previous resubmission.

The PBAC previously considered the likely optimistic between-attack utilities that were applied to be a key issue in the in the economic evaluation (paragraph 7.13, lanadelumab PSD, July 2020). The ESC acknowledged that the QALY framework can be challenging, particularly when determining the benefits associated with treatments which prevent acute attacks, but noted that the resubmission had not addressed the concerns raised in the July 2020 consideration.

6.19 The utilities applied in the base case (Nordenfelt 2017)[§] were based on a small sample size. In the base case, the utility value for a 'moderate' level of Angioedema Activity Score for 28 consecutive days (AAS28) (0.64, based on 9 patients) was applied to 83.2% of patients in the SOC arm, with a utility of 0.80 for a 'low' level of AAS28 (based on 14 patients) applied to the remaining 16.8%. In contrast, the utility value for 'zero' level of AAS28 (0.88, based on 24 patients) was applied to all patients in the lanadelumab arm. The ESC noted that both the Institute for Clinical and Economic Review (USA) and the Canadian Agency for Drugs and Technologies in Health (CADTH) used a model that predicted utility based on age and number of attacks.

6.20 As in the previous resubmission, the number of attacks per 28 days was rounded down to a whole number (i.e. 0 decimal places). Patients with no attacks per 28 days were assigned a 'between-attack' utility of 0.88, while patients with one attack per 28 days and those experiencing two or more attacks per 28 days were assigned 'between-attack' utilities of 0.80 and 0.64, respectively. As a result of rounding down the number of attacks, in the base case analysis, all patients in the lanadelumab arm were assumed to be attack free over the entire 12-month time horizon. This amplified the magnitude of the treatment effect, favouring lanadelumab. The ESC considered that the rounding down of attacks was inappropriate. The revised economic model presented in the pre-PBAC response removed rounding from the number of attacks per 28 days (see paragraph 6.29).

6.21 The key drivers of the model are summarised below.

Table 6: Key drivers of the model

Description	Method/Value	Impact
The mean cost/patient/year for lanadelumab	Assuming that 100% of patients receive the reduced dose of 300 mg Q4W, with a mean number of 13 doses per patient	High, favours lanadelumab
The distribution of baseline attack frequency	Baseline attack frequencies of 107 patient-years that had been dispensed ≥ 24 injections of icatibant over a 12-month period, as reported in PBS data.	High, higher frequency favours lanadelumab
The 'between-attack' (background) utility values	Assigned to each member of the cohort on the basis of the estimated number of attacks per 28 days	High, approach favours lanadelumab
Efficacy of lanadelumab versus SOC	Based on the RRR for HAE attacks requiring acute treatment in the lanadelumab 300 mg Q2W arm of HELP, rather than using the RRR for the Q4W arm, consistent with the costings for lanadelumab.	High, favours lanadelumab

Source: Spreadsheet 'Inputs' Excel workbook 'LANA_Resubmission_Minor_HAE_Sec3_CUA'

[§] Nordenfelt P, Nilsson M*, et al.* Health-related quality of life in relation to disease activity in adults with hereditary angioedema in Sweden. *Allergy Asthma Proc*. 2017; 38 (6):447-55.

HAE = hereditary angioedema; Q2W = every 2 weeks; Q4W = every 4 weeks; RRR = relative risk reduction; SOC = standard of care.

6.22 The results of the economic analysis, in terms of both the cost per treated attack avoided and the cost per QALY gained, are presented below. The results of the analysis presented in the July 2020 resubmission have been provided for comparison.

Table 7: Results of the economic evaluation (effective price lanadelumab)

Outcome for ICER	Costs			Outcomes			ICER
	LANA	SOC	Inc	LANA	SOC	Inc	
Current resubmission							
HAE attacks requiring acute treatment	$[redacted]	$130,428	$[redacted]	7.0	54.8	-47.8	$[redacted][6] per treated HAE attack avoided
QALYs gained	**$[redacted][1]**	**$130,428**	**$[redacted][2]**	**0.8731**	**0.5826**	**0.2906**	**$[redacted][4]/QALY**
July 2020 resubmission							
HAE attacks requiring acute treatment	$[redacted]	$185,205	$[redacted]	7.0	55.0	-48.0	$[redacted][6] per treated HAE attack avoided
QALYs gained	$[redacted][1]	$185,205	$[redacted][3]	0.8658	0.0599	0.2959	$[redacted][5]/QALY

Source: Table 13 and Table 14 of the resubmission

HAE = hereditary angioedema; ICER = incremental cost-effectiveness ratio; Inc = increment; LANA = lanadelumab; QALY = quality-adjusted life-year; SOC = standard of care.

Blue shading indicates data previously seen by the PBAC.

The redacted values correspond to the following ranges:

[1] *$155,000 to < $255,000/QALY gained*

[2] *$25,000 to < $35,000/QALY gained*

[3] *$15,000 to < $25,000/QALY gained*

[4] *$95,000 to < $115,000/QALY gained*

[5] *$45,000 to < $55,000/QALY gained*

[6] *$0 to < $5,000/treated HAE attack avoided*

6.23 The resubmission noted that the ICER in the base case of the model increased to $95,000 to < $115,000/QALY in the revised economic model, compared with $45,000 to < $55,000/QALY in the July 2020 resubmission, despite a reduction in the lanadelumab cost per patient (due to the proposed RSA) and a similar number of attacks avoided. This was almost entirely due to a 65% reduction in the price of icatibant on the PBS since the previous resubmission, resulting in a 31% decrease in the cost savings associated with the cost of treating acute HAE attacks.

6.24 The results of sensitivity analyses are summarised below.

Table 8: Results of the sensitivity analyses (effective price lanadelumab)

Analyses		Incremental cost	Incremental QALY	ICER $/QALY gained
Base case		**$**	**0.2906**	**$**
Analyses presented in the resubmission for purposes of RSA				
1	Dose of lanadelumab (Base case 100% Q4W, 13 doses/year) 100% Q2W (26 doses/year)	$	0.2906	$
2	Baseline attack rate (base case ≥24 per annum) Patients with baseline attack rate ≥12 to <24 per annum,	$	0.0841	$
1 + 2	Baseline attack rate ≥12 to <24 per annum and 100% lanadelumab Q2W	$	0.0841	$
Univariate sensitivity analyses performed during the evaluation				
3	PBS data used to determine distribution of baseline attacks (Base case data for 2016-2019, 107 patient years) • Data from 2012 to 2019, 141 patient years	$	0.2910	$
4	Baseline attack rate, per year (base case 54.8 per year)			
	a) 24 (threshold for eligibility)	$	0.1139	$
	b) 30	$	0.2824	$
	c) 40	$	0.2966	$
	d) 50	$	0.3107	$
	e) 60	$	0.3248	$
	f) 70	-$	0.3390	-$
	g) Excluding patients with ≥96 attacks per year[a]	$	0.2746	$
5	Cost of lanadelumab (Base case 13 doses/patient/year)			
	Disregarding RSA[b]			
	a) 23% Q2W, 77% Q4W (mean 15.98 doses/year)[c]	$	0.2906	$
	b) 50% Q2W, 50% Q4W (mean 19.5 doses/year)	$	0.2906	$
	c) 75% Q2W, 25% Q4W (mean 22.75 doses/year)	$	0.2906	$
	d) 100% Q2W (mean 26 doses/year)	$	0.2906	$
	Applying RSA (use above 13 doses rebated at %)[d]			
	e) 23% Q2W, 77% Q4W ($152,779/patient/year)	$	0.2906	$
	f) 50% Q2W, 50% Q4W ($164,227/patient/year)	$	0.2906	$
	g) 75% Q2W, 25% Q4W ($174,788/patient/year)	$	0.2906	$
	h) 100% Q2W ($/patient/year)	$	0.2906	$
6	LANA efficacy (Base case: 300 mg Q2W RRR 0.87299)			
	a) 300 mg Q4W arm HELP trial: RRR 0.74169	$	0.2461	$
	b) Weighted 77%:23% Q4W:Q2W (RRR 0.77176)[c]	$	0.2514	$
7	'Between-attack' utility values (Base case: no attacks 0.88; 1 attack/28 days 0.80; ≥2 attacks/28 days 0.64) • 0.825 for 0 attacks, decreasing by 0.0043 for each additional attack per 28 days (Nordenfelt 2014)[e]	$	0.0930	$
8	Calculation of attacks/28 days (Base case rounded down)[f] • No rounding	$	0.2375	$
9	QALY loss for HAE attack (base case: LANA 0.00099, SOC 0.00154) • No disutilities applied	$	0.2131	$
10	Imputation of PBS icatibant data reported as <5 syringes (base case imputed with 1 syringe) • > 5 replaced with 2 • > 5 replaced with 4	$ $	0.2965 0.3001	$ $

Source: Table 16 of the resubmission; Excel workbook "LANA_REsubmisison_HAE_Sec3_CUA"

AAS = Angioedema Activity Score; CI = confidence interval; HAE = hereditary angioedema; ICER = incremental cost-effectiveness ratio; LANA = lanadelumab; Q2W = every 2 weeks; Q4W = every 4 weeks; QALY = quality-adjusted life-years; RRR = relative risk reduction; RSA = risk sharing arrangement; SOC = standard of care.

[a] As these patients experienced, on average, more than 8 attacks per month, routine prophylaxis with C1-INH may be a more appropriate comparator than SOC.

[b] Calculated by applying the cost of lanadelumab per patient per year in Cell C38 of the 'Inputs' spreadsheet in the Excel workbook for Section 3, assuming a DPMQ of $[redacted] for 2 syringes ($[redacted]*2 + $161.16)

[c] Distribution of doses assumed in the July 2020 resubmission.

[d] Cost of lanadelumab per patient per year: first 6.5 scripts (13 syringes) = ($[redacted]*2 + $161.16)*6.5 = $143.105, all subsequent scripts (2 syringes per script) = ($[redacted]*2*0.29 + $161.16)*x%*6.5 = $[redacted]*x%*6.5, where x% = proportion of patients receiving the Q2W dose regimen, $[redacted] is the proposed effective EMP for lanadelumab, and $161.16 is the mark-ups and fees. The total cost was applied in Cell C38 of the 'Inputs' spreadsheet in the Excel workbook for Section 3.

[e] Both the Institute of Clinical and Economic Review and CADTH applied the formula: Utility = 0.825 – 0.043*#attacks – 0.2205* age, where #attacks was the mean number of attacks per month, and age was measured in increments of 10 years. This formula was based on the results reported in Nordenfelt 2014.

[f] In the base case, the number of attacks per 28 days was calculated from the number of attacks per year and rounded down to 0 decimal places (i.e. a whole number). The 'between-attack' utility was based on the number of treated attacks per 28 days, while the 'in-attack' disutility and the costs associated with treating acute attacks were based on the number of attacks per 12 months.

Figures in italics were calculated during the evaluation using the Excel workbook "LANA_REsubmisison_HAE_Sec3_CUA"

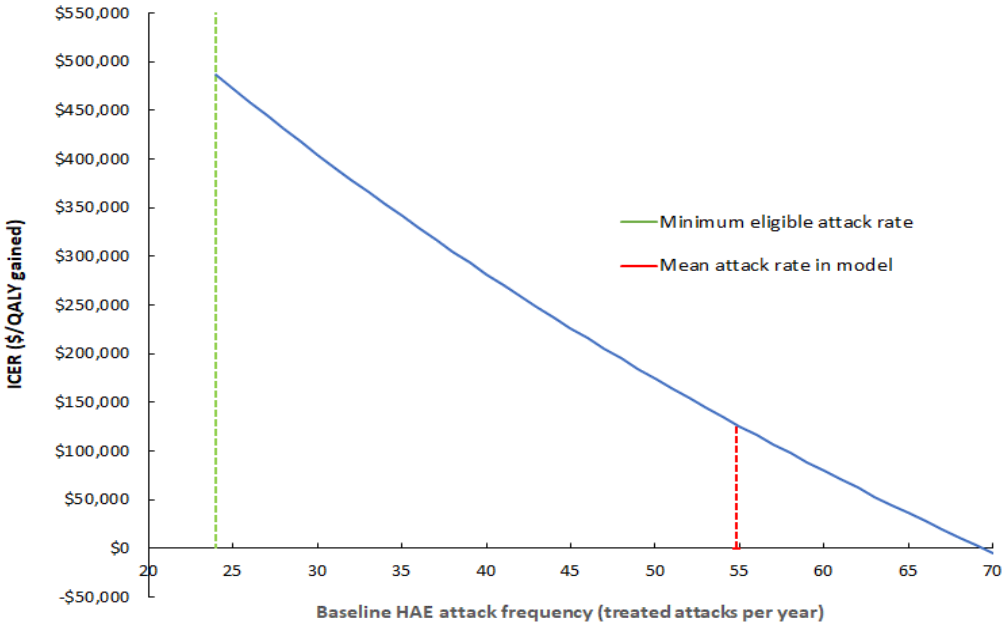
The redacted values correspond to the following ranges:

[1] $95,000 to < $115,000/QALY gained
[2] $555,000 to < $655,000/QALY gained
[3] > $1,055,000/QALY gained
[4] $755,000 to < $855,000/QALY gained
[5] $255,000 to < $355,000/QALY gained
[6] $155,000 to < $255,000/QALY gained
[7] $55,000 to < $75,000/QALY gained
[8] $0 to < $5,000/QALY gained
[9] $455,000 to < $555,000/QALY gained
[10] $115,000 to < $135,000/QALY gained
[11] $135,000 to < $155,000/QALY gained

6.25 As in the previous resubmission, the sensitivity analyses demonstrate the considerable uncertainty in the estimated cost-effectiveness of lanadelumab for prophylaxis of HAE attacks. In particular, the results of the model were highly sensitive to the baseline rate of treated attacks, the proportion of patients who would receive the lower dose of lanadelumab, and the 'between-attack' utilities. With the proposed rebate of [redacted]% applied to use of lanadelumab above 13 syringes/patient/year, the ICER increased to $115,000 to < $135,000/QALY when 23% of patients were assumed to receive the more frequent dose regimen of 300 mg Q2W.

6.26 The impact of the baseline frequency of treated HAE attacks on the cost-effectiveness of lanadelumab for the prophylaxis of HAE attacks, without rounding of the number of attacks per 28 days, is illustrated below (Figure 1).

Figure 1: Impact of the baseline frequency of treated HAE attacks on the outcome of the economic model (without rounding of the number of attacks per 28 days) (effective price lanadelumab)



Source: Constructed during preparation of the ESC advice from data in the Excel workbook 'LANA_Resubmission_Minor_HAE_Sec3_CUA'"
ICER = incremental cost-effectiveness ratio; HAE = hereditary angioedema; QALY = quality-adjusted life-year
Note: the mean number of attacks requiring acute treatment in the model was 54.8 attacks per year; the mean number of attacks requiring acute treatment in the placebo arm of HELP was 1.64 per 4 weeks (approximately 21 per year).

6.27 Without rounding, the ICER in patients experiencing a baseline of 24 treated attacks per year was $355,000 to < $455,000/QALY gained. The ICER fell below $95,000 to < $115,000/QALY gained at a baseline attack frequency of 58 treated attacks per year, with lanadelumab continuing to be dominant at baseline rates of > 69 attacks per year.

6.28 The ESC advised that there were some outstanding issues of uncertainty with the model. The ESC considered that a respecified base case should include no rounding in the calculation of the number of attacks per 28 days, apply the weighted lanadelumab efficacy (0.77176), and apply that 23% of patients received Q2W dosing. The ICER for this scenario was $155,000 to < $255,000/QALY. The ESC further considered that if the rebate for use in excess of 13 injections per year was less than [redacted]%, then the cost of the additional injections should be included in the model. If the rebate was [redacted]% as proposed in the resubmission, the ICER would increase to $255,000 to < $355,000/QALY. The ESC further noted the optimistic between-attack utilities continued to be applied as per the previous submission. The ESC considered that a price reduction would likely be required to obtain an ICER which was acceptable.

6.29 The pre-PBAC response provided an updated economic model which incorporated the two changes suggested by ESC, (i) removal of rounding in calculation of the number of attacks for 28 days; and (ii) application of the weighted lanadelumab efficacy. As noted above, these changes resulted in an ICER of $155,000 to < $255,000 per QALY. The

pre-PBAC response then applied a price reduction of 17% to the effective DPMQ of lanadelumab, resulting in an ICER of $95,000 to < $115,000 per QALY.

Drug cost/patient/year

6.30 The resubmission estimated the expected cost of lanadelumab per patient per year, estimated as $[redacted]. This was based on a proposed effective dispensed price of $[redacted] (AEMP = $[redacted]) for a 300 mg syringe, assuming the cost per patient is capped at the cost of 13 syringes per year. This compared to an estimated cost/patient per year of $[redacted] in the previous submission, based on a proposed dispensed price of $[redacted] (AEMP $[redacted]) for one 300 mg vial of lanadelumab, and a weighted mean of [redacted] vials per patient per year.

Estimated PBS usage & financial implications

6.31 DUSC did not consider this resubmission.

6.32 The resubmission estimated the use of lanadelumab in two patient populations, consistent with the two initial treatment restrictions proposed:

- Patients who are currently treated with ODT (i.e. are not receiving routine prophylaxis with C1-INH) who qualify for lanadelumab under the proposed restriction requiring patients to have experienced at least 12 treated acute attacks of HAE within a period of 6 months (referred to as the SOC population in the resubmission). This would include patients eligible under the initial treatment 1 restriction and the grandfather provision (initial treatment 3); and
- Patients receiving C1-INH as routine prophylaxis of HAE when lanadelumab is listed, who choose to switch to lanadelumab (referred to as the C1-INH population in the resubmission).

6.33 The key changes in the inputs between the current resubmission and the resubmission considered by the PBAC in July 2020 are summarised in the table below. The July 2020 resubmission effectively applied prevalence estimates as incidence estimates; this has been corrected in the current resubmission.

Table 9: Key differences in the inputs for the financial estimates between the resubmissions

Parameter	July 2020 resubmission	Current resubmission	Justification in resubmission
Attack distribution and frequency (data source)	Incident cohort (2012-2015) N=11 patients Mean 55.0 attacks/patient/ year Proportion ≥ 24 attacks per year: 4.5%	Prevalent cohort (2016-2019) N=107 patient years Mean 54.8 attacks/patient/ year Proportion ≥ 24 attacks per year: 13.86%	DUSC data provided upon request from the sponsor
Annual discontinuation	15%	0%	Application of prevalence estimate versus incidence
Proportion of patients on Q4W regimen (syringes per year)	77.1% (weighted mean 15.98 syringes/patient/year)	100.0% (13.00 syringes/patient/year)	Assumption made in the economic model, and risk proposed to be managed via a RSA. The ESC noted that use of greater than 13 syringes per patient per year would incur a cost due to the proposed RSA rebate being less than 100%.
Icatibant syringe price	DPMQ: $2,455.87 AEMP: $2,303.75	DPMQ: $850.66 AEMP: $756.70	PBS item 1976B
Initial C1-INH 500 IU vial price	2021: $971.15 per vial	2022: $990.56 per vial	Annual 2% increase based on precedent
Average annual icatibant use	33.60 syringes per year	31.13 syringes per year	Updated underlying DUSC data

Source: Table 1 of the resubmission

AEMP = approved ex-manufacturer price; C1-INH = C-1 esterase inhibitor; DPMQ = dispensed price for maximum quantity; DUSC = Drug Utilisation Sub-Committee; IU = international units; RSA = risk sharing arrangement

6.34 The sources of data used in the utilisation and financial estimates are summarised below.

Table 10: Data sources and parameter values applied in the utilisation and financial estimates

Data	Value applied and source	Comment
Eligible population		
SOC population (patients who experience ≥ 12 treated HAE attacks within 6 months)		
Prevalent HAE patients	Yr 1: 500 to < 5,000 to Yr 6: 500 to < 5,000 ABS Population – 3222.0 Series B Prevalence estimate from literature review (2 in 100,000)	This source was reasonable.
% HAE patients eligible (≥ 12 treated attacks in 6 months)	13.86%, DUSC Secretariat analysis of the PBS data for icatibant patients prescribed ≥24 injections within a calendar year (2016-2019)	Icatibant utilisation data may not represent a reliable proxy for determining the number of treated HAE attacks (see below)
Uptake rate	[redacted]% in all years, Assumption	The ESC considered that uptake in Year 1 may be overestimated.
C1-INH population (patients receiving C1-INH prophylaxis when lanadelumab is listed and who switch to lanadelumab)		
Total patients who would receive C1-INH as prophylaxis in the absence of lanadelumab	Yr 1: < 500 to Yr 6: < 500 NBA data on the utilisation of IV Berinert from July 2016 to June 2019 (number of vials dispensed). Assumed [redacted]% of use of IV C1-INH use for prophylaxis Number of patients derived assuming an average of 3.52 vials per dose, 104 doses per year (366 vials per patient per year).	The proportion of use of IV C1-INH that was for routine prophylaxis was a major source of uncertainty
Uptake rate in patients receiving C1-INH when lanadelumab is listed.	Yr 1: [redacted]%, Yr 2: [redacted]% and then Yr 3 – 6: [redacted]% Assumption The resubmission assumed [redacted]% uptake in Year 1 and a further [redacted]% of those not switching in Year 1 were assumed to switch in Year 2 (i.e. [redacted]% x [redacted]% = [redacted]%), resulting in a cumulative uptake of [redacted]% in Years 2-6.	Given the recent listing of the subcutaneous preparation of C1-INH on the NBA's NPL, the uptake of lanadelumab in these patients may be lower than assumed in the resubmission.
Number of syringes		
Syringes dispensed	Yr 1: 500 to < 5,000 to Yr 6: 500 to < 5,000 Assumed that all patients received 13 syringes per year.	The resubmission capped the cost per patient at 13 doses per year. This was intended to reflect the proposed RSA. However, the proposed RSA only covered [redacted]% of the costs for any usage beyond 13 doses per year.

Source: Section 4.3 of the resubmission; Excel workbook 'Electronic_Files_LANA_Resubmission_Minor_HAE_Sec4_BIM'
ABS = Australian Bureau of Statistics; C1-INH = C1 esterase inhibitor; HAE = hereditary angioedema; IU = international units; IV = intravenous; LANA = lanadelumab; NBA = National Blood Authority; NPL = National Product List; RSA = risk sharing arrangement; SOC = standard of care; Yr = Year.

6.35 As in the previous resubmission, based on the results of a literature search, a prevalence of 2 in 100,000 was used to estimate the number of patients with HAE in Australia. The resubmission's estimate of the number of HAE patients in Australia ranged from 500 to < 5,000 in Year 1 of listing (2022) to 500 to < 5,000 in Year 6. The June 2015 DUSC review of icatibant usage found that the number of patients supplied icatibant was much lower than expected. The economic analysis estimated that between < 500and < 500 patients were dispensed at least one injection of icatibant in each calendar year from 2016 to 2019. This suggests that the prevalence of HAE in the Australian population has been overestimated.

6.36 The proportion of SOC patients eligible for lanadelumab was based on PBS data, in which the resubmission estimated that an average of 13.86% of patients received ≥ 24 injections of icatibant within a calendar year over the four years from 2016 to 2019. The previous resubmission assumed that only 4.5% of HAE patients would meet the

eligibility criteria for lanadelumab; however, this estimate was based on only 11 patients.

6.37 The proportion of HAE patients who would be eligible for PBS-subsidised lanadelumab was a major source of uncertainty in the financial estimates. The ESC considered that using the number of icatibant injections dispensed per patient in each calendar year to estimate the proportion of patients likely to meet the eligibility criterion, was subject to a number of limitations including that:

- the number of icatibant injections dispensed may not be a reliable proxy for the number of treated HAE attacks, as patients may require more than one injection of icatibant per attack, and some patients may have multiple injections on hand in anticipation of attacks;
- the number of patients receiving a given number of injections was often reported as < 5, therefore, the exact proportion of patients receiving ≥ 24 icatibant injections within a calendar year was not known;
- in the current clinical setting, where danazol is no longer available, the mean number of attacks per patient per year may be higher than during the period over which the data were collected, where a proportion of patients were likely to have been receiving danazol for routine oral prophylaxis of attacks;
- the data will have included patients receiving C1-INH as routine prophylaxis. This may have resulted in an underestimation of the proportion of patients who would have been dispensed ≥ 24 injections per calendar year;
- the dataset may not be representative of the entire HAE population, and it was not possible to determine whether particular patients were repeatedly meeting the criterion each year, or whether the qualifying patients differed from year to year.

The initial point regarding the reliability of the number of icatibant injections dispensed as a proxy for the number of treated HAE attacks, could potentially overestimate the proportion of patients meeting the eligibility criterion. Most of the remaining assumptions applied in the estimates potentially underestimated the number of SOC patients likely to be eligible. The overall direction and extent of bias was unclear.

6.38 The resubmission assumed that, as patients transition in and out of eligibility, the proportion of HAE patients treated each year would remain constant (13.9%). It claimed that this approach accounted for the concerns regarding patients continuing treatment beyond the intent of the continuation criteria by only accounting for patients at a point in time when they are deriving appropriate clinical benefit, as it was similar to requiring patients to re-qualify for treatment each year. In practice, as patients who qualify in any given year and respond to treatment are eligible to continue treatment in subsequent years, the proportion of HAE patients treated with lanadelumab would be expected to increase over time. Therefore, the resubmission's

approach is likely to underestimate the number of patients likely to be treated in Years 2-6 of listing.

6.39 The ESC considered that the uptake rate of [redacted]% was likely overestimated, particularly in Year 1. The ESC considered that uptake in the eligible patient population in Year 1, excluding grandfather patients, would be approximately [redacted]%. The pre-PBAC response applied an uptake in Year 1 of [redacted]% in the revised RSA (see paragraph 6.58).

6.40 The market share approach used to estimate lanadelumab utilisation in the C1-INH population was based on the utilisation of C1-INH reimbursed under the National Blood Authority (NBA). For the base case of the financial analysis, the resubmission used the patient estimates for the C1-INH population from the July 2020 resubmission.

6.41 The resubmission proposed that existing C1-INH patients have the option to switch to lanadelumab over the first two years of PBS listing, and that the access criteria and item code could be deleted after that time, in line with similar arrangements for grandfathered patients. The PBAC noted that there was no clear rationale as to why patients should only be able to switch from C1-INH to lanadelumab in the first two years following listing of lanadelumab on the PBS and considered that the Initial 2 listing should not be deleted without further consideration by the PBAC.

6.42 With the listing of the subcutaneous preparation of C1-INH on the NBA's National Product List (NPL; previously only IV C1-INH was available), uptake of lanadelumab in patients eligible for prophylactic treatment with C1-INH is likely to be lower than assumed in the resubmission.

6.43 The cost of lanadelumab per patient per year was based on the lanadelumab 300 mg Q4W regimen (13 syringes/patient/year), at an annual effective dispensed price per patient of $[redacted]. The resubmission justified this assumption based on the RSA proposed in the resubmission. The resubmission proposed a rebate of only [redacted]% on utilisation of lanadelumab above this level. Furthermore, a cost of 13 syringes of lanadelumab was also applied to C1-INH population. However, the resubmission stated that the proposed RSA excluded patients transitioning from C1-INH routine prophylaxis. Therefore, the cost per patient for lanadelumab was underestimated for this patient cohort. This was updated in the revised RSA presented in the pre-PBAC response.

6.44 As in the previous resubmission, the impact of lanadelumab on the use of icatibant was calculated based on the effectiveness of lanadelumab in reducing acute HAE attacks, and the expected attack frequency in patients who would receive lanadelumab but who, in the absence of lanadelumab, would not have received prophylaxis with C1-INH. The average number of icatibant syringes dispensed per patient per year (31.13) was based on patients from the PBS icatibant data who were dispensed ≥ 24 but ≤ 48 icatibant syringes within a calendar year. While the rationale behind the choice of 48 attacks as the upper limit was not apparent, it was a conservative approach.

6.45 The resubmission estimated the cost savings to the Australian Government health budget resulting from a reduction in the use of C1-INH, for treatment of acute HAE attacks in the SOC population, and for switching from prophylactic C1-INH to lanadelumab in the C1-INH population.

6.46 The estimated use of lanadelumab and its financial implications are summarised below. The resubmission stated that the SOC population included patients eligible under the Initial treatment - 1 restriction and the grandfather provision (Initial treatment - 3). The resubmission stated that there were currently 12 patients receiving lanadelumab via a patient access program.

Table 11: Estimated use and financial implication (effective dispensed price for lanadelumab)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated financial implication for lanadelumab - SOC population (patients experiencing ≥ 12 attacks over 6 months)						
Patients treated	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Syringes dispensed	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
Net PBS/RPBS cost	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][4]	$[redacted][4]	$[redacted][4]
Estimated financial implication for lanadelumab - C1-INH population (patients switching from C1-INH prophylaxis)						
Patients treated	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Syringes dispensed	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Net PBS/RPBS cost	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]
Total treated population						
Total patients treated	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Total syringes dispensed	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
Net PBS/RPBS cost	**$**[redacted][4]	**$**[redacted][4]	**$**[redacted][4]	**$**[redacted][4]	**$**[redacted][4]	**$**[redacted][4]
Estimated financial implication for icatibant (patients dispensed ≥ 24 but ≤ 48 icatibant syringes within a calendar year)						
Background attacks (mean 31.13/patient/year)[a]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
Attacks prevented[b]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
Icatibant injections avoided[c]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
Net savings PBS/RPBS[d]	**$**[redacted][3]	**$**[redacted][3]	**$**[redacted][3]	**$**[redacted][3]	**$**[redacted][3]	**$**[redacted][3]
Net financial implications						
Net cost to PBS/RPBS	**$**[redacted][4]	**$**[redacted][4]	**$**[redacted][4]	**$**[redacted][4]	**$**[redacted][4]	**$**[redacted][4]
Cost saving to the Australian Government health budget[e]	-$[redacted][3]	-$[redacted][3]	-$[redacted][4]	-$[redacted][4]	-$[redacted][4]	-$[redacted][4]
Net implications for the Australian Government health budget	**$**[redacted][3]	**$**[redacted][3]	**$**[redacted][3]	**$**[redacted][3]	**$**[redacted][3]	**$**[redacted][3]
Estimates from the July 2020 resubmission						
Net PBS/RPBS cost	$[redacted][3]	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]
Re-analysis[f]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][4]

Source: : Table 33, p41 of the resubmission; Table 16, paragraph 6.76, lanadelumab, PBAC Public Summary Document (PSD), July 2020 PBAC meeting

C1-INH = C1 esterase inhibitor; SOC = standard of care.

[a] Based on patients dispensed ≤ 24 but ≤ 48 icatibant syringes within a calendar year.

[b] Assuming an 87% reduction due to the efficacy of lanadelumab. This was the efficacy in the lanadelumab 300 mg Q2W arm of HELP.

[c] 0.65 injections per prevented attack, based on patient survey.

[d] DPMQ for icatibant (PBS item 1976B): $850.66

[e] Savings to the Australian Government health budget from reduced funding for IV C1-INH through the National Blood Agreement, assuming the federal government is responsible for 63% of funding and state/territory governments are responsible for the remaining 37%.

[f] Re-analysis performed during the evaluation, based on the prevalent population, with no allowance for discontinuations.

Blue shading indicates data previously seen by the PBAC.

The redacted values correspond to the following ranges:

[1] *< 500*

[2] *500 to < 5,000*

[3] *$0 to < $10 million*

[4] *$10 million to < $20 million*

6.47 The total cost to the PBS/RPBS of listing lanadelumab was estimated to be $10 million to < $20 million in Year 6, and a total of approximately $80 to < $90 million in the first 6 years of listing. The ESC noted that although the patient numbers had been revised from the July 2020 resubmission, the total estimated cost to the PBS/RPBS over the first 6 years of listing was similar ($80 million to < $90 million).

6.48 The ESC considered that the estimated net cost to the PBS/RPBS was highly uncertain as the:

- exact prevalence of HAE in Australia is unknown and using the number of icatibant injections dispensed as a proxy for the number of treated HAE attacks was subject to a number of limitations.
- absence of indication-specific data for the utilisation of IV C1-INH through the National Blood Agreement, and the limited data available since the listing of the subcutaneous preparation, meant that the number of patients currently receiving C1-INH for routine prophylaxis cannot be reliably estimated.
- cost per patient per year for lanadelumab was underestimated in both populations, as the resubmission failed to incorporate the cost for the proportion of patients who would receive the 300 mg Q2W dosage.

6.49 Patients assumed to switch from C1-INH prophylaxis to lanadelumab would result in savings to the Australian Government health budget as the cost per patient per year for IV C1-INH (approximately $0 to < $10 million) was higher than the estimated effective cost per patient per year for lanadelumab ($0 to < $10 million for 13 injections and $0 to < $10 million for 26 injections. As the number of patients switching from C1-INH routine prophylaxis to lanadelumab may be overestimated, these potential savings may not be realised.

6.50 Due to the limitations outlined above, the estimated net implications for government health budgets were highly uncertain. There was still considerable potential for use outside the intended population, and the uncertainty regarding the dosage regimen that would be used in clinical practice remains as an issue. The resubmission proposed to address these issues via an RSA (see below).

Financial Management – Risk Sharing Arrangements

6.51 In July 2020 the PBAC noted the RSA caps proposed in the pre-PBAC response, but considered that further work was required to ensure the RSA caps would appropriately manage the risks of: (1) use in cost-ineffective populations; and (2) the uncertainty in the dosage regimens. The PBAC also considered that a [redacted]% rebate should apply for any usage above the total cap (paragraphs 7.16 and 7.17, lanadelumab PSD, July 2020).

6.52 The resubmission proposed a RSA in which the expenditure cap was based on the estimated size of the eligible SOC population (patients experiencing ≥ 24 treated attacks over 12 months), assuming that all patients receive 13 doses per annum. The RSA excluded patients transitioning from routine prophylaxis with C1-INH and proposed a [redacted]% rebate on utilisation of lanadelumab above the expenditure cap.

6.53 The resubmission justified the proposed [redacted]% rebate on the basis that, for patients dispensed ≥ 12 to < 24 icatibant syringes per annum (i.e. use beyond the intended population), the base case ICER of $95,000 to < $115,000/QALY could be achieved if a

[redacted]% discount to the cost of lanadelumab was applied. The [redacted]% rebate on the AEMP of lanadelumab was based on the assumption that all patients received lanadelumab Q4W. Under the proposed RSA, financial risks to the PBS still remain due to the potential for i) use in patients experiencing fewer than 12 treated attacks over 6 months, ii) use in patients who continue treatment when no longer receiving appropriate benefit, and iii) patients receiving lanadelumab Q2W dosing.

6.54 Given that the ICER for the SOC population derived in the economic analysis was based on the assumption that the cost of lanadelumab would be capped at 13 doses per patient per year, the ESC considered that all expenditure resulting from utilisation above this level would need to be rebated at [redacted]% to maintain this level of cost-effectiveness, particularly as a rebate of less than [redacted]% was at odds with the economic model which assumed that cost was based solely on monthly treatment.

6.55 In addition, it would not be possible to differentiate additional utilisation in patients outside the intended population (i.e. in patients experiencing fewer than 12 treated attacks over 6 months) from use in patients receiving the more frequent dose regimen of 300 mg lanadelumab Q2W. Therefore, to mitigate the risk of the Australian Government of costs for non-cost-effective use, a [redacted]% rebate was required. The PSCR stated that if expenditure is being exceeded because treatment is being used in lower attack frequency patients, then it is appropriate to rebate [redacted]% to ensure these additional patients are as cost-effective as the eligible population. The PSCR also stated that it was important to note that the proposed caps do not allow for the risk of eligible patients continuing treatment in subsequent treatment years. The ESC noted that whether this rebate would mean that patients were 'equally cost-effective as the eligible population' would depend on a number of factors including frequency of HAE attacks. Overall, the ESC did not consider that the claim of cost-effectiveness being achieved with the [redacted]% rebate in this population had been adequately supported and considered a [redacted]% rebate to be appropriate.

6.56 The resubmission noted that the RSA excluded patients transitioning from C1-INH routine prophylaxis, as the size of this patient cohort was uncertain. It stated that C1-INH patients should be allowed to transition to lanadelumab by virtue of lanadelumab being cost-effective in these patients if they were not receiving C1-INH. The resubmission did not state how the exclusion of C1-INH patients would be implemented, although the resubmission proposed a separate restriction for patients initiating lanadelumab following C1-INH prophylaxis, it did not address how utilisation by these patients would be tracked separately in the continuing treatment phase for the purposes of administering the RSA. The PSCR proposed that the Authority Required – written listing should include a record of whether patients were prophylaxis naïve (SOC group) or had previously received prophylaxis (C1-INH group). While the ESC considered that utilisation for the two groups could be tracked against the proposed separate PBS initial treatment restrictions, this would be difficult to implement for continuing prescriptions. Further, the ESC considered that not including a subset of patients in the proposed RSA was not consistent with providing a robust

RSA for the overall listing of lanadelumab, and that the risks being managed for the SOC population, i.e. dose frequency and leakage to less severe populations, were also relevant to those patients switching from C1-INH.

6.57 The ESC considered that a two tier RSA may be appropriate in which Tier 1 was based on the number of patients estimated to switch from C1-INH (< 500 patients in Year 1 increasing to < 500 patients in Year 6; Table 11) and Tier 2 was based on the number of patients estimated to switch from SOC (< 500 patients in Year 1 increasing to < 500 patients in Year 6; Table 11). The cost of lanadelumab for use between Tiers 1 and 2 should reflect the price that is determined to be cost-effective as per paragraph 6.29. The rebate applied for use beyond Tier 2 should consider the risk of use of more than 13 injections per year and the risk of use in patients with ≤24 attacks per year. The ESC considered that the rebate for use beyond Tier 2 should be [redacted]% as outlined above in paragraph 6.59.

6.58 The pre-PBAC response proposed a two-tier RSA that was based on the framework suggested by the ESC (paragraph 6.57). The revised expenditure caps applied the updated effective DPMQ ($[redacted] for one syringe) and assumed that all patients received 13 doses per year (i.e. Q4W dosing). Tier 1 was based on the predicted expenditure from patients switching from C1-INH. Tier 2 included grandfather patients and those estimated to switch from SOC (uptake in Year 1 was reduced from [redacted]% to [redacted]%). Expenditure between Tiers 1 and 2 was rebated at [redacted]% to reflect the updated acceptable level of cost-effectiveness (see paragraph 6.29). The rebate for use beyond Tier 2 was [redacted]% - see Table 12.

Table 12: Revised RSA expenditure thresholds (calculated using effective DPMQ)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Notes
C1-INH patients							
C1-INH patients [A]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	-
Syringes/year [B]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	= [A]*13 syringes/ year
Tier 1 PBS effective expenditure cap	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	= [B]*$[redacted]
SOC patients							
Grandfather patients	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	-
Eligible SOC patients [C]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	-
Uptake rate [D]	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	Uptake in Year 1 decreased
Non-grandfather SOC patients	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	= [C]*[D]
Total SOC patients [E]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	-
Syringes/year [F]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	= [E]*13 syringes/ year
PBS expenditure [G]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][4]	$[redacted][4]	$[redacted][4]	= [F]*$[redacted]
SOC effective expenditure	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	= [G]*(1-[redacted]% rebate)
Combined							
Total treated patients	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[A]+[E]
Total syringes/year	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[B]+[F]
Tier 2 PBS effective expenditure cap	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]	[B]+[G]

Source: Table 1 of pre-PBAC response

CI-INH = C1-esterase inhibitor; DPMQ = dispensed price for maximum quantity; PBS = Pharmaceutical Benefits Scheme; RSA = risk sharing arrangement; SOC = standard of care; SPA = special pricing arrangement

The redacted values correspond to the following ranges:

[1] *< 500*

[2] *500 to < 5,000*

[3] *$0 to < $10 million*

[4] *$10 million to < $20 million*

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 prophylaxis of recurrent attacks of hereditary angioedema (HAE). The PBAC, noting that danazol was no longer available in Australia and that there was currently no intervention available for patients with an attack frequency of 8 per month or fewer, considered that there was a high clinical need for effective and tolerable prophylactic therapies for these HAE patients. The PBAC considered that for some patients, lanadelumab provided a substantial clinical benefit in terms of a reduction in HAE attack frequency versus standard of care (SOC). The PBAC noted that although the updated economic model resulted in an incremental cost effectiveness ratio (ICER) which remained uncertain, the associated financial risk was managed by the proposed Risk Sharing Arrangement (RSA) in this small and definable patient population.

7.2 The PBAC acknowledged the consumer comments which were strongly supportive of listing lanadelumab and which described the substantial quality of life benefits of the prophylactic treatment.

7.3 The PBAC noted that the resubmission presented revised proposed restrictions. The PBAC, noting the outcomes of the stakeholder meeting, considered that although the number of baseline HAE attacks (12 in 6 months) for lanadelumab eligibility remained unchanged in the initial treatment restriction for patients who did not qualify for routine prophylaxis with National Blood Authority funded C1-INH (i.e. Initial treatment - 1), this was reasonable. The PBAC considered that the revised criteria for the attacks to be acute, which was defined as those that required targeted on-demand therapy, was appropriate. Additionally, the PBAC considered that the requested restriction changes in the pre-PBAC response, including that the initial restrictions be Authority Required – non-immediate assessment, that supply be restricted to patients 12 years of age and older and that the maximum quantity per restriction be reduced to one syringe per month, were appropriate.

7.4 The PBAC recalled that the key clinical evidence, as provided by the HELP trial, supported the clinical claim that lanadelumab was superior to SOC in terms of comparative effectiveness, but that there was residual uncertainty in the magnitude of the benefit due to the small patient numbers in the trial and potential applicability issues. The PBAC also recalled that the four weekly (Q4W) regimen did not demonstrate a significant difference in efficacy compared to the two weekly (Q2W) regimen. In terms of safety, the PBAC recalled that although lanadelumab demonstrated inferior safety compared to SOC, it was well tolerated.

7.5 The PBAC noted that the resubmission presented a revised economic model for lanadelumab versus SOC that applied updated data to estimate the baseline HAE attack frequency and applied the cost of the lanadelumab 300 mg Q4W regimen (i.e. 13 doses per year) to all patients. Further, the PBAC noted that the pre-PBAC response provided an updated model which incorporated two changes suggested by ESC, i) removal of rounding in calculation of the number of attacks for 28 days; and (ii)

application of the weighted lanadelumab efficacy. In addition, the pre-PBAC response model applied a price reduction of 17% to the effective DPMQ of lanadelumab, resulting in an ICER of $95,000 to < $115,000 per QALY. The PBAC considered that the ICER was reasonable, although noted that it likely remained underestimated, due to the continued application of optimistic between-attack utilities, and uncertain, as it remained highly sensitive to the baseline rate of treated attacks.

7.6 The PBAC noted the revisions to the utilisation and financial estimates presented in the resubmission and the pre-PBAC response. The PBAC considered that the revised total number of patients treated each year (< 500 in Year 1 increasing to < 500 in Year 6) was reasonable.

7.7 The PBAC noted that the pre-PBAC response presented a revised RSA which was based on advice provided by the ESC (see paragraph 6.58). The PBAC was highly confident that that the revised two-tier RSA, which included an assumption that all patients received 13 doses per year (i.e. Q4W dosing), adequately mitigated the risk of expenditure exceeding the estimated financial impact.

7.8 The PBAC noted that the resubmission proposed a grandfather restriction and advised that this should only be in effect for 12 months.

7.9 The PBAC advised that lanadelumab is not suitable for prescribing by nurse practitioners.

7.10 The PBAC advised that lanadelumab should not be exempt from the Early Supply Rule.

7.11 The PBAC advised, that under Section 101(3BA) of the *National Health Act 1953*, lanadelumab should not be treated as interchangeable on an individual patient basis with any other drug.

7.12 The PBAC found that the criteria prescribed by the National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2009 for Pricing Pathway A were met. Specifically, the PBAC found that in the circumstances of its recommendation for lanadelumab:

a) The treatment is expected to provide a substantial and clinically relevant improvement in efficacy over standard of care;

b) The treatment is expected to address a high and urgent unmet clinical need;

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 been met.

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

Outcome:
Recommended

8 Recommended listing

8.1 Add new item:

Name, Restriction, Manner of administration and form	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Proprietary Name
LANADELUMAB					
lanadelumab 300 mg/2 mL injection, 1 x 2 mL syringe	NEW	1	1	5	Takhzyro

Initial 1:

	Category / Program: GENERAL – General Schedule (Code GE)
	Prescriber type: ☒Medical Practitioners
	Restriction Level / Method: ☒Authority Required (in writing)– Postal/HPOS Upload
	Episodicity: Chronic treatment of
	Condition: hereditary angioedema Types 1 or 2
	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)
	Treatment criteria:
	Must be treated by a clinical immunologist or a specialist allergist
	AND
	Clinical criteria:
	Patient must have experienced at least 12 treated acute attacks of hereditary angioedema within a 6 months 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 PBS-subsidised in combination with a C1-esterase inhibitor concentrate
	Population criteria:
	Patient must be aged 12 years or older
	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. EST 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
	Administrative Advice: No increase in the maximum number of repeats may be authorised
	Administrative Advice: Special pricing arrangements apply

Initial 2:

	Category / Program: GENERAL – General Schedule (Code GE)
	Prescriber type: ☒Medical Practitioners
	Restriction Level / Method: ☒Authority Required – (in writing)– Postal/HPOS Upload
	Episodicity: Chronic treatment of
	Condition: hereditary angioedema Types 1 or 2
	Indication: Chronic treatment of hereditary angioedema Types 1 or 2
	Treatment Phase: Initial 2: New patient (commencing from National Blood Authority-funded C1-INH)
	Treatment criteria:
	Must be treated by a clinical immunologist or a specialist allergist
	AND
	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
	Clinical criteria:
	The treatment must not be PBS-subsidised in combination with a C1-esterase inhibitor concentrate
	Population criteria:
	Patient must be aged 12 years or older
	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. EST 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
	Administrative Advice: No increase in the maximum number of repeats may be authorised
	Administrative Advice: Special pricing arrangements apply

Grandfather restriction

	Category / Program: GENERAL – General Schedule (Code GE)
	Prescriber type: ☒Medical Practitioners
	Restriction Level / Method: ☒Authority Required – (in writing)– Postal/HPOS Upload
	Episodicity: Chronic treatment of
	Condition: hereditary angioedema Types 1 or 2
	Indication: Chronic treatment of hereditary angioedema Types 1 or 2
	Treatment Phase: Initial 3: Grandfather (commencing from non-PBS-subsidised treatment with this drug)
	Treatment criteria:
	Must be treated by a clinical immunologist or a specialist allergist
	AND
	Clinical criteria:
	Patient must have previously received non-PBS subsidised treatment with this drug as routine prophylaxis for hereditary angioedema prior to [listing date]
	AND
	Clinical criteria:
	Patient must have experienced at least 12 treated acute attacks of hereditary angioedema within a 6 months period prior to commencing treatment with this drug
	AND
	Clinical criteria:
	The treatment must not be PBS-subsidised in combination with a C1-esterase inhibitor concentrate
	Population criteria:
	Patient must be aged 12 years or older
	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 number of treated acute attacks of hereditary angioedema with 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. EST 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
	Administrative Advice: A patient may only qualify for PBS-subsidised treatment under this restriction once in a lifetime
	Administrative Advice: This Grandfather restriction will cease to operate 12 months after the date specified in the clinical criteria
	Administrative Advice: No increase in the maximum number of repeats may be authorised
	Administrative Advice: Special pricing arrangements apply

Name, Restriction, Manner of administration and form	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Proprietary Name
LANADELUMAB					
lanadelumab 300 mg/2 mL injection 1 x 2 mL syringe	NEW	1	1	5	Takhzyro

Continuing treatment Restriction Summary [new]:

	Category / Program: GENERAL – General Schedule (Code GE)
	Prescriber type: ☒Medical Practitioners
	Restriction Level / Method: ☒Authority Required –Telephone/OPA immediate assessment
	Episodicity: Chronic treatment of
	Condition: hereditary angioedema Types 1 or 2
	Indication: Chronic treatment of hereditary angioedema Types 1 or 2
	Treatment Phase: Continuing preventative treatment
	Treatment criteria:
	Must be treated by, or in consultation with, a clinical immunologist or specialist allergist
	AND
	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, as judged by the treating clinician
	Population criteria:
	Patient must be aged 12 years or older
	Prescriber instruction: 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
	Prescriber instruction: For the purposes of administering this restriction, an adequate response is a reduction of the number of acute attacks of hereditary angioedema of a severity necessitating immediate medical intervention with either (i) icatibant, or (ii) C1-esterase inhibitor concentrate in comparison to baseline. The details of the reduction must be documented in the patient's medical records for auditing purposes.
	Administrative Advice: (applicable to telephone/online authority approvals) 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 888 33
	Administrative Advice: No increase in the maximum number of repeats may be authorised
	Administrative Advice: Special pricing arrangements apply

This restriction 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.