7.02 LANADELUMAB, Solution for injection 300 mg in 2 mL, Takhzyro®, Shire Australia Pty Ltd.

1 Purpose of resubmission

1.1 The resubmission requested a Section 85, Authority Required listing for lanadelumab as routine (long term) prophylaxis of recurrent attacks of hereditary angioedema (HAE).

1.2 The requested listing was based on a cost-utility analysis (CUA) of lanadelumab compared with standard of care (SOC) in patients with HAE. The previous submission was based on a cost-minimisation analysis of lanadelumab compared with intravenous (IV) C1 esterase inhibitor (C1-INH) in patients with HAE. The key components of the clinical issue addressed by the resubmission are summarised below (in comparison with those presented in the previous submission).

Table 1: Key components of the clinical issue as presented in the resubmission (clinical issue components for original submission included for comparison).

Component	Description	
	Previous: July 2019 PBAC consideration	**Current: July 2020 PBAC consideration**
Population	Patients with HAE treated with on-demand treatment 12 or more times within a 6-month period, despite receiving a maximum tolerated dose of danazol (unless clinically inappropriate) as routine prophylaxis for HAE. (This proposed population did not align with the population for the comparator, C1-INH, which is restricted to patients who experience 8 or more attacks per month.) The requested restriction also included patients who have experienced a life-threatening HAE attack within the previous 12 months despite receiving the maximum tolerated dose of danazol (unless danazol is clinically inappropriate)	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
Intervention	Lanadelumab subcutaneous injection.	Lanadelumab subcutaneous injection.
Comparator	Intravenous C1-INH (Berinert®), currently available for routine prophylaxis in HAE on the "National Blood Authority National Product and Services List (NPSL)", under the National Blood Agreement	SOC for HAE, which comprises use of ODT (icatibant or IV C1-INH) with oral routine prophylaxis
Outcomes	HAE attack rate HAE attack rate requiring acute treatment Percentage responder	HAE attack rate HAE attack rate requiring acute treatment Percentage responder
Clinical claim	Non-inferiority vs C1-INH.	Superiority versus SOC[a]

Source: Table 1, Lanadelumab HAE PSD, July 2019 PBAC meeting and Table 9 of the resubmission
C1-INH = C1 esterase inhibitor; HAE = hereditary angioedema; SOC = standard of care; ODT = on-demand treatment; IV = intravenous.
[a] The resubmission also made an economic claim that lanadelumab is associated with reduced use of ODT and better quality of life (QoL).

2 Background

Registration status

2.1 Lanadelumab 300 mg/2 mL (solution for injection and pre-filled syringe formulations) are TGA-registered for the following indication: the routine prevention of recurrent attacks of HAE (C1-INH deficiency or dysfunction) in patients aged 12 years and older.

2.2 The recommended starting dose in the lanadelumab approved Product Information is 300 mg lanadelumab every 2 weeks (Q2W). In patients who are stably attack free on treatment, a dose reduction to 300 mg every 4 weeks (Q4W) may be considered, especially in patients with low weight.

2.3 This dosing aligns with the EMA and FDA. The TGA Delegate's Overview) states 'the (TGA) evaluator is of the view that the optimal dosing regimen has not been determined as the pivotal study was not designed to compare the treatment effect within the 3 randomised lanadelumab treatment arms. The evaluator considers that the small numerical differences in the three arms in the HELP trial reflect small numbers and the inherent intra-individual variability in the pattern of HAE attacks rather than greater efficacy with one arm, and there is insufficient data to recommend any one regimen over the other two dose regimens'. The TGA Delegate's Overview stated that taking into account factors including the safety profile for patients <50 kg, the general 'benign' safety profile of lanadelumab, and the efficacy of lanadelumab 300 mg Q2W for patients with all weight groups, the Delegate was inclined to align with the dose recommendations accepted by the EMA.

Previous PBAC consideration

2.4 This was the second submission requesting listing of lanadelumab for routine prevention of recurrent attacks of HAE. A major submission requesting listing for the same indication was considered at the July 2019 PBAC meeting.

Table 2: Summary of key matters of concern

Component	Matter of concern	How the resubmission addresses it
Clinical place in therapy	The PBAC considered the clinical role of lanadelumab in the context of the clinical need in patients who experienced fewer than eight attacks per [month], the ease of administration of a SC formulation and the clinical evidence for lanadelumab. As such, the PBAC advised that the appropriate clinical role for lanadelumab is broader than the population who are eligible for IV C1-INH (Para 7.5, July 2019 PSD).	Addressed. The proposed restriction and patient population in the resubmission reflected the PBAC comments. The proposed patient population comprised patients experiencing at least 12 treated acute attacks of HAE within a period of 6 months prior to commencement of treatment.

Component	Matter of concern	How the resubmission addresses it
Comparator	C1-INH was not the appropriate comparator. The PBAC considered that standard of care (on-demand treatment plus oral routine prophylaxis) was the appropriate comparator in patients who experience fewer than eight attacks per month, which the PBAC considered would represent the majority of patients with a broader listing (Para 7.7, July 2019 PSD).	Addressed. The resubmission nominated SOC, comprising of ODT with oral routine prophylaxis. There is some uncertainty pertaining to the current supply of danazol which has been deleted from the market in Australia by the supplier Mylan. Danazol is still currently listed on the PBS and resupply may recur in the near future. For patients with ≥ 8 attack/month, C1-INH would be the appropriate comparator. There could also be some use of C1-INH in patients with < 8 attacks/month given the number of attacks per month may vary over time and this may be difficult to monitor.
Clinical evidence	The clinical trial of lanadelumab (the HELP trial) lacked applicability to a population solely comprising patients with eight or more attacks per month (Para 7.9, July 2019 PSD).	Partially addressed. The requested population (≥ 12 attacks within 6 months) is now broader than the NBA criteria for accessing C1-INH (≥ 8 attacks per month) the comparator nominated in the previous submission. The HELP trial which included patients with ≥ 1 attack per month is now more applicable in this regard. However, patients in HELP were not permitted to use routine prophylaxis during the randomised phase.
Economic evaluation	A cost-minimisation analysis was inappropriate given: the indirect evidence presented did not demonstrate non-inferior effectiveness of lanadelumab versus C1-INH (SC or IV); and the PBAC's advice that the appropriate clinical role of lanadelumab is broader than the population in whom C1-INH was considered cost-effective by MSAC (Para 7.10, July 2019 PSD).	Addressed. The resubmission presented a cost-effectiveness analysis based on direct evidence comparing lanadelumab with placebo.
Financial estimates	The financial estimates would need to be revised to account for use in a broader population (Para 7.12, July 2019 PSD).	Addressed. The financial estimates were revised to reflect the broader patient population.
	The number of vials per patient was underestimated because it relied on the assumption that [redacted]% of patients would only require a steady state dose of lanadelumab 300 mg every 4 weeks (Para 7.13, July 2019 PBAC PSD).	Not addressed. Both the economic analysis and the financial estimates assumed that [redacted]% of patients would only require lanadelumab 300 mg every 4 weeks.
	The number of eligible patients who access IV C1-INH for routine prophylaxis was uncertain given the lack of data about utilisation by indication and the potential for leakage in patients who experienced fewer than eight attacks per month (Para 7.11, July 2019 PSD).	Not addressed. The resubmission still relied on this data to estimate a proportion of the eligible patient population.

Source: Sections 1-4 of the resubmission; Lanadelumab PSD, July 2019 PBAC meeting; Lanadelumab PSD July 2019 PBAC meeting.
C1-INH = C1 esterase inhibitor; HAE = hereditary angioedema; IV = intravenous; ODT = on-demand treatment; PSD = Public Summary Document; SC = subcutaneous; SOC = standard of care.

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

3 Requested listing

3.1 The listing requested in the submission is presented below, along with changes suggested by the Secretariat (suggested additions are in italics and deletions are in strikethrough).

Name, restriction, manner of administration, form	Maximum quantity (units)	No. of repeats	Dispensed price for maximum quantity [a]	Proprietary name and manufacturer
LANADELUMAB 300 mg/2 mL ~~solution for subcutaneous~~ injection, 2 mL vial 300 mg/2 mL solution ~~for subcutaneous injection~~, pre-filled syringe	2	5	Published: $[redacted] Effective $[redacted]	Takhzyro® Shire Australia Pty Ltd / Takeda Pharmaceuticals Australia Pty Ltd

[a] Published AEMP: $[redacted] for 1 x 300 mg vial; Effective AEMP (SPA): $[redacted] for 1 x 300 mg vial. Proposed SPA is equivalent to a [redacted]% discount to the published AEMP.

Initial 1 treatment Restriction Summary [new]:

Category / Program: GENERAL – General Schedule (Code GE)
Prescriber type: ☒Medical Practitioners
Restriction typel / Method: ☒~~Authority Required – non-immediate/delayed assessment by Medicare (In-writing only via mail/postal service or electronic upload to Hobart)~~ ☒*Authority Required – immediate/real time assessment by Services Australia (telephone/online)*
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 *– preventative treatment for a patient starting therapy with this drug for the first time*
Treatment criteria:
Must be treated by *at least one of a:* ~~a specialist~~ *clinical* immunologist~~; or~~ */ specialist allergist*
~~Must be treated by a specialist immunologist and allergist~~
AND
Clinical criteria:
Patient must have experienced at least 12 treated acute attacks of ~~HAE~~ *hereditary angioedema* within ~~a period of~~ *the* 6 month~~s~~ prior to commenc~~ement~~*ing* ~~of~~ treatment *with this drug*
AND
Clinical criteria:
Patient must be intolerant ~~or insufficiently protected by~~ *of* oral routine prophylaxis*; or*
Patient must be insufficiently protected by oral routine prophylaxis, as judged by the treating clinician
AND
Clinical criteria:
The treatment must not be PBS-subsidised in combination with a C1-esterase inhibitor concentrate
Prescribing Instructions: *For the purposes of administering this restriction, acute attacks of hereditary angioedema are those of a severity necessitating immediate medical intervention* ~~*The authority application must be made in writing and must include:*~~ ~~*a) completed authority prescription form; and*~~ ~~*b) a completed hereditary angioedema Initial - 1 PBS authority application form which includes*~~ *The baseline number of treated acute attacks of ~~HAE~~ hereditary angioedema within the 6 months prior to initiating treatment must be documented in the patient's medical records for auditing purposes.*

An intolerance of oral routine prophylaxis must be of a severity requiring permanent treatment discontinuation. Details of the intolerance (e.g. name of oral prophylaxis, date of adverse reaction, nature of reaction) must be documented in the patient's medical records for auditing purposes.
~~**Prescribing Instructions:**~~ ~~This medicine is not PBS subsidised for use in combination with C1-esterase inhibitor~~
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 quantity or number of units may be authorised.
Administrative Advice: No increase in the maximum number of repeats may be authorised
Administrative Advice: *Special pricing arrangements apply*

Continuing treatment Restriction Summary [new]:

Category / Program: GENERAL – General Schedule (Code GE)
Prescriber type: ☒Medical Practitioners
Restriction type / Method: ~~☒Authority Required – non-immediate/delayed assessment by Medicare (In-writing only via mail/postal service or electronic upload to Hobart)~~ ☒*Authority Required – immediate/real time assessment by Services Australia (telephone/online)*
Episodicity: *Chronic treatment of*
Condition: hereditary angioedema ~~(HAE)~~ *Types 1 or 2*
PBS Indication: *Chronic treatment of* hereditary angioedema ~~(HAE)~~ *Types 1 or 2*
Treatment Phase: Continuing *preventative treatment*
Clinical criteria:
Patient must have previously received PBS-subsidised ~~initial~~ treatment with this drug ~~as routine prophylaxis for HAE~~, *for this condition*
AND
Clinical criteria:
~~Patient must have demonstrated or maintained a treatment response to treatment with this drug for this condition~~ *Patient must have demonstrated or sustained an adequate response to PBS-subsidised treatment with this drug for this condition*
AND
Clinical criteria:
This medicine is not PBS subsidised for use in combination with C1-esterase inhibitor concentrate
Treatment criteria:
~~Must be treated by a specialist immunologist; or~~ ~~Must be treated by a specialist immunologist and allergist; or~~ ~~Must be treated in consultation with a specialist immunologist or immunologist and allergist.~~ *Must be treated by a specialist allergist or clinical immunologist, or in consultation with a specialist allergist or clinical immunologist*
AND
Prescribing Instructions: ~~For patients initiating under the Initial – 1 restriction,~~ *A* treatment response is defined as a reduction of 50% *or more* from baseline in the number of treated acute attacks of HAE ~~per month~~ *over the previous six months* ~~compared to baseline~~.
~~This medicine is not PBS subsidised for use in combination with C1-esterase inhibitor~~
~~In patients who are attack free on treatment, a dose reduction to 300 mg lanadelumab every 4 weeks may be considered.~~
Patients must not receive more than 6 months of treatment under this restriction
A patient who fails to respond to a course of PBS-subsidised lanadelumab as routine prophylaxis for HAE will not be eligible to receive further PBS-subsidised treatment with this drug for this condition
Administrative Advice: No increase in the maximum quantity or number of units may be authorised
Administrative Advice: No increase in the maximum number of repeats may be authorised
Administrative Advice: *Special pricing arrangements apply*

Initial 2 (commencing from NBA-funded C1-INH) restriction

Category / Program: GENERAL – General Schedule (Code GE)

Prescriber type: ☒Medical Practitioners
Restriction type / Method: ~~☒Authority Required – In Writing~~ ☒*Authority Required – immediate/real time assessment by Services Australia (telephone/online)*
Indication: Hereditary Angioedema (HAE)
Treatment Phase: Initial – 2 *preventative treatment for a patient commencing from National Blood Authority-funded C1-INH*
Clinical criteria:
Patient must be currently receiving C1-esterase inhibitor through the National Blood Authority as routine prophylaxis for HAE
Treatment criteria:
Must be treated by *at least one of a:* ~~a specialist~~ *clinical* immunologist~~; or~~ */ specialist allergist*
~~Must be treated by a specialist immunologist and allergist~~
AND
Clinical criteria:
The treatment must not be PBS-subsidised in combination with a C1-esterase inhibitor concentrate
~~**Prescribing Instructions:**~~ ~~The authority application must be made in writing and must include:~~ ~~a) completed authority prescription form; and~~ ~~b) a completed hereditary angioedema Initial – 2 PBS authority application form which includes:~~ ~~Evidence of prior use of C1-esterase inhibitor funded through the National Blood Authority as routine prophylaxis including formulation and dose.~~
~~This medicine is not PBS subsidised for use in combination with C1-esterase inhibitor~~
Administrative Advice: *Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 33*
Administrative Advice: No increase in the maximum quantity or number of units may be authorised
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: ☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Restriction type / Method: ~~☒Authority Required – non-immediate/delayed assessment by Services Australia (In-writing only via mail/postal service or electronic upload to Hobart)~~ ☒*Authority Required – immediate/real time assessment by Services Australia (telephone/online)*
Administrative Advice: No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised *Special pricing arrangements apply*
Indication: Hereditary Angioedema (HAE)
Treatment Phase: Initial - Grandfather treatment *(patient initiated on non-PBS subsidised treatment).*
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 a period of 6 months prior to commencement of treatment AND Patient must be intolerant or insufficiently protected by oral routine prophylaxis ~~OR~~ ~~Patient must have previously received C1-esterase inhibitor through the National Blood Authority as routine prophylaxis for HAE~~
AND
Treatment criteria:
Must be treated by *at least one of a:* ~~a specialist~~ *clinical* immunologist~~; or~~ */ specialist allergist*
~~Must be treated by a specialist immunologist and allergist~~
Clinical criteria:

The treatment must not be PBS-subsidised in combination with a C1-esterase inhibitor concentrate
AND
Prescribing 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 acute attacks of ~~HAE~~ hereditary angioedema within the 6 months prior to initiating treatment must be documented in the patient's medical records for auditing purposes.* *An intolerance of oral routine prophylaxis must be of a severity requiring permanent treatment discontinuation. Details of the intolerance (e.g. name of oral prophylaxis, date of adverse reaction, nature of reaction) must be documented in the patient's medical records for auditing purposes.* ~~The authority application must be made in writing and must include:~~ ~~a) completed authority prescription form; and~~ ~~b) a completed hereditary angioedema Grandfather PBS authority application -Supporting Information Form which includes:~~ • ~~Documentation of treatment start date; and~~ • ~~Baseline measurement of the number of treated acute attacks of HAE within the 6 months prior to initiating treatment; or~~ • ~~Evidence of prior use of C1 esterase inhibitor funded through the National Blood Authority as routine prophylaxis, including formulation and dose~~
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*
~~This medicine is not PBS subsidised for use in combination with C1 esterase inhibitor~~
A patient may only qualify for PBS-subsidised treatment under this restriction once in a lifetime.
This Grandfather restriction will cease to operate 12 months after the date specified in the clinical criteria

3.2 The proposed effective price was 50% lower than in the previous submission.

3.3 The resubmission proposed PBS-listing of lanadelumab for patients who have experienced at least 12 treated acute attacks of HAE within a period of 6 months. The wording does not specify either the site or the severity of the attack to be treated and further definition of an acute attack may be required. The PBAC considered that consultation with clinical experts would be required to determine the appropriate minimum number of attacks at baseline to ensure lanadelumab use is targeted to a sufficiently high risk population required further definition. Further definition around 'treated acute attacks' may also be required.

3.4 In contrast to the previous submission, the requested restriction in the resubmission did not specify eligibility on the basis of having experienced a life-threatening HAE attack within the previous 12 months. While this was consistent with the key clinical evidence presented in the resubmission, the PBAC considered that further work was required to ensure that the restriction targeted use to the most appropriate high risk population.

3.5 To be eligible for continuing treatment after 6 months, the resubmission proposed that a patient must have had a ≥ 50% reduction in the rate of HAE attacks per month, compared with baseline. The previous submission stated this aligned with the pivotal clinical trial of lanadelumab (HELP), in which all patients randomised to 300 mg every 2 weeks achieved at least a 50% reduction in attack rate compared to baseline. Potential issues with this approach include that it: 1) does not account for attack

severity; 2) relies on patient self-reporting; 3) may be difficult to reliably assess; and 4) it was not clear whether the reduced level of attacks (compared with baseline) would need to be maintained every 6 months. The PBAC considered that the rationale for the proposed continuation criteria was unclear and further work was required to ensure ongoing use is targeted to patients deriving appropriate clinical benefit from lanadelumab.

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

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. Type 3 is characterised by normal C1-INH functional levels. The key trial of lanadelumab (the HELP trial) enrolled patients with HAE Types 1 and 2 and the TGA-registered indication specifies use in patients with C1-INH deficiency or dysfunction.

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 on-demand therapy (ODT) such as icatibant or IV C1-INH. Other patients have multiple attacks per month or per week, necessitating prophylactic treatment. Oral prophylactic therapies include danazol and tranexamic acid. Where oral therapies are ineffective or clinically inappropriate, 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)[1].

4.6 Access to C1-INH (Berinert®) through the NPL is restricted to this group of patients (patients who experience eight or more attacks per month), as the MSAC advised that C1-INH would only be cost-effective in patients with very severe HAE. The MSAC PSD states that MSAC 'concluded that it had low confidence that the use of C1-INH offered clinically important improvements for pre-procedural and routine prophylaxis of

[1] 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).

hereditary angioedema', and its recommendation was based on 'restricting access to only those patients with a very high attack frequency', which the MSAC estimated would be limited to 8 patients per year'. Further, the PBAC previously noted that the MSAC's assessment of the cost-effectiveness of C1-INH for routine prophylaxis appeared to have used the price proposed for the acute attack indication (which was cost-minimised against icatibant), (Paragraph 7.14, Lanadelumab PSD, July 2019 PBAC meeting).

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

5 Comparator

5.1 IV C1-INH, which is funded under the National Blood Agreement as routine prophylaxis for patients who experience ≥ eight attacks per month, was nominated as the main comparator in the previous submission. The resubmission nominated SOC, which comprises ODT (icatibant or IV C1-INH) with oral routine prophylaxis, as the main comparator.

5.2 The nominated comparator of SOC in the resubmission is consistent with previous advice provided by the July 2019 PBAC which stated 'SOC (on-demand treatment plus oral routine prophylaxis) was the appropriate comparator in patients who experience fewer than eight attacks per month, which the PBAC considered would represent the majority of patients with a broader listing' (paragraph 7.7, Lanadelumab PSD, July 2019 PBAC meeting).

5.3 The Australasian Society of Clinical Immunology and Allergy (ASCIA) 2020 HAE Position Paper (p11) state that danazol and tranexamic acid have historically been used for long term prophylaxis, however use is limited by side effects and relative lack of efficacy, respectively. The resubmission noted that there may be a supply issue with danazol in Australia. If danazol becomes unavailable, the only oral prophylactic available on the PBS would be tranexamic acid. Shortage in supply of oral prophylactics may result in an increased supply/use of ODT (higher risk of attacks in the absence of routine oral prophylaxis).

5.4 For patients who experience eight or more attacks per month, C1-INH (supplied and funded through the NBA) may also be an appropriate comparator. Although C1-INH may an appropriate comparator for patients who experience eight or more attacks per month, this is expected to represent only a small proportion of patients.

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

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 (24), health care professionals (3) and an organisation (1) via the Consumer Comments facility on the PBS website. The comments described the debilitating nature of HAE attacks and the significant impact that attacks can have on quality of life. The comments also described the unpredictable and potentially life-threatening nature of attacks.

6.3 The comments were strongly supportive of listing lanadelumab, describing its efficacy and ease of administration. The comments noted the adverse events, lack of efficacy and supply issues with danazol, and the difficulties of administering C1-INH. The comments also described the need for effective treatments for patients who have a high burden of disease but do not meet the eligibility requirements for C1-INH through the NBA.

Clinical trial

6.4 The resubmission was based on one head-to-head, randomised, double-blind, controlled trial (HELP), which compared three dose regimens of lanadelumab (as routine prophylaxis) + ODT with placebo (no routine prophylaxis) + ODT, in patients with Types 1 and 2 HAE. The HELP trial has previously been considered by the PBAC. There were four treatment arms in HELP:

- Lanadelumab 300 mg SC Q2W (N=27),
- Lanadelumab 300 mg SC Q4W (N=29),
- Lanadelumab 150 mg SC Q4W (N=28) (not registered), and
- Placebo SC Q2W (N=41).

6.5 Details of the trial presented in the resubmission are provided in the table below.

Table 3: Trials and associated reports presented in the resubmission

Trial ID	Protocol title/ Publication title	Publication citation
Included trials		
HELP	Clinical Study Report: HELP Study®: A Multicenter, Randomised, Double-Blind, Placebo-Controlled Efficacy and Safety Study to Evaluate DX-2930 For Long-Term Prophylaxis Against Acute Attacks of Hereditary Angioedema (HAE).	September 2017
	Hereditary Angioedema (HAE) – Assessment of Patient Reported Outcome Data from the DX-2930- 03 HELP Study®– Primary Objectives.	August 2017
	Banerji A, Riedl M, Berstein JA, et al. Effect of lanadelumab Compared with Placebo on Prevention of Hereditary Angioedema Attacks.	JAMA 2018; 320(20): 2108-2121.

Source: Table 22, p32 of the resubmission

6.6 The key features of the direct randomised trial are summarised in the table below.

Table 4: Key features of the included evidence

Trial		N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
Lanadelumab trial							
HELP	300 mg lanadelumab SC Q2W[a]	27	R, DB 26 weeks	Low	≥ 1 attack / month (investigator-confirmed attacks) No restriction on line of therapy[c]	Number of investigator-confirmed HAE attacks during the treatment period and number of attacks requiring acute treatment	Used
	300 mg lanadelumab SC Q4W[a]	29					Used
	150 mg lanadelumab SC Q4W[a,b]	28					Not used
	PBO SC Q2W[a]	41					Used

Source: Section 2.3-2.4, pp33-47 of the resubmission.

DB = double blind; HAE = hereditary angioedema; PBO = placebo; Q2W = every 2 weeks; Q4W = every 4 weeks; R = randomised; SC = subcutaneous.

[a] To maintain blinding, placebo doses were administered in between doses of lanadelumab for patients randomised to lanadelumab 150 mg or 300 mg 4 weekly. Also for each 300 mg dose of lanadelumab, each subject received a total of 2 mL divided into 2 separate 1.0 mL injections. For each 150 mg dose of lanadelumab, each subject received a 1.0 mL injection of lanadelumab and a 1.0 mL injection of placebo. For each placebo dose, each subject received a total of 2 mL, divided into 2 separate injections on placebo.

[b] Lanadelumab 150 mg every 4 weeks was not a TGA registered dose.

The TGA recommended starting dose for lanadelumab is 300 mg Q2W. In patients who are stably attack free on treatment, the dose frequency may be reduced to 300 mg Q4W. Although both the Q2W and Q4W regimens of lanadelumab 300 mg were assessed in HELP, the impact of reducing the dosing frequency from Q2W to Q4W was not assessed as modifications to the lanadelumab fixed dose regimes were not allowed.

[c] Patients were not permitted to use routine prophylactic therapy (C1-INH, attenuated androgens, or antifibrinolytics) for HAE

Comparative effectiveness

6.7 The results of the primary outcome and key secondary outcomes are summarised below.

Table 5: HELP trial: Primary and key secondary outcomes among patients with hereditary angioedema attacks[a]

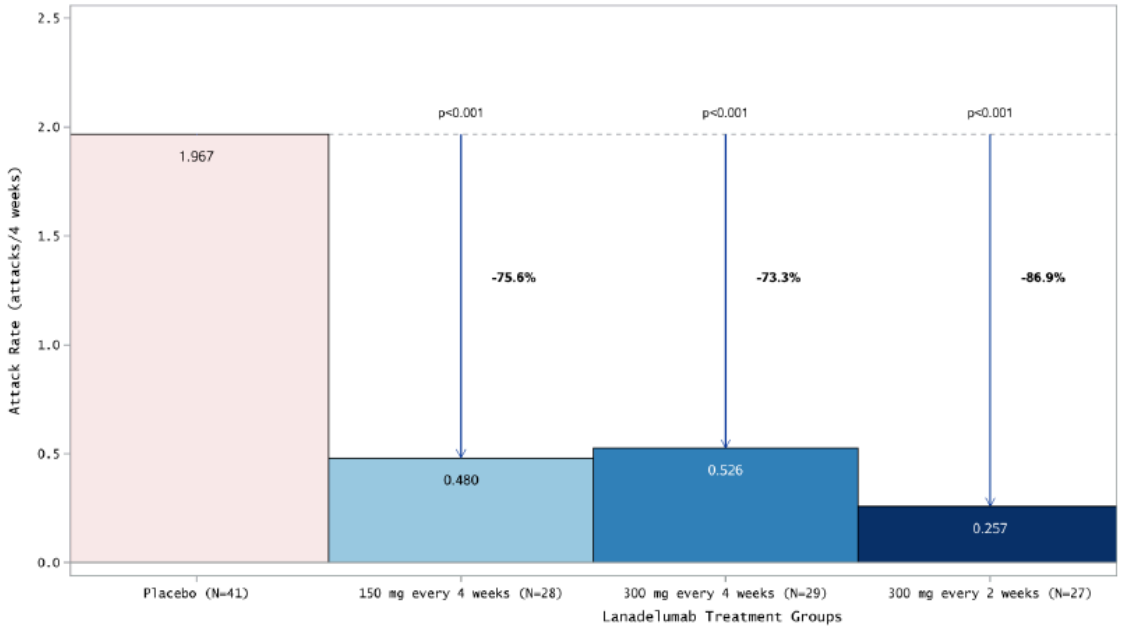
Treatment measure	Lanadelumab SC			PBO SC
	150 mg Q4W	300 mg Q4W	300 mg Q2W	
N	28	29	27	41
Attack rate during run-in period–Attacks per month				
Mean (SD) Median (Min, Max)	3.22 (1.83) 3.2 (1.0, 6.7)	3.71 (2.51) 3.00 (1.00, 10.50)	3.52 (2.33) 3.11 (1.00, 9.00)	4.02 (3.27) 3.00 (1.00, 14.70)
Primary outcome primary analysis				
Attack rate during treatment period (Day 0 to endpoint Day 182 (or 26 weeks follow up endpoint) Attacks per month				
Mean (95% CI) [b,c]	0.48 (0.31, 0.73)	0.53 (0.36, 0.77)	0.26 (0.15, 0.46)	1.97 (1.64, 2.36)
Difference vs. PBO, (95% CI)[d] p-value	**−1.49 (−1.90, −1.08)** **<0.001**	**-1.44 (-1.84, -1.04)** **<0.001**	**-1.71 (-2.09, -1.33)** **<0.001**	-
Rate ratio vs. PBO, (95% CI) p-value[e]	**0.24 (0.15, 0.39)** **<0.001**	**0.27 (0.18, 0.41)** **<0.001**	**0.13 (0.07, 0.24)** **<0.001**	-
% reduction vs. PBO, (95% CI)[f]	**-75.6 (-84.7, -61.2)** **<0.001**	**-73.3 (-82.4, -59.5)** **<0.001**	**-86.9 (-92.8, -76.2,)** **<0.001**	-
Secondary outcomes				
Number of attacks requiring rescue or acute treatment during treatment period per month (Day 0 to Day 182)				
Mean (95% CI) [b,c]	0.31 (0.18 to 0.53)	0.42 (0.28, 0.65)	0.21 (0.11, 0.40)	1.64 (1.34, 2.01)
Mean difference vs. PBO, (95% CI)[d], p-value	**−1.32 (−1.69, −0.95)** **<0.001**	**-1.21 (-1.58, -0.85)** **<0.001**	**-1.43 (-1.78, -1.07)** **<0.001**	-
Rate ratio vs. PBO, (95% CI) p-value[e]	**0.19 (0.11, 0.34)** **<0.001**	**0.26 (0.16, 0.41)** **<0.001**	**0.13 (0.07, 0.25)** **<0.001**	-
% reduction vs. PBO, (95% CI)	**-80.84 (-89.2, -66.1)**	**-74.2 (-83.70, -59.0)**	**-87.3 (-93.50, -75.2)**	-
No. of moderate or severe attacks during treatment period per month (Day 0 to Day 182)				
Mean (95% CI) [b,c]	0.36 (0.22 to 0.58)	0.32 (0.20, 0.53)	0.20 (0.11, 0.39)	1.22 (0.97, 1.52)
Mean difference vs. PBO, (95% CI)[d] p-value	**−0.86 (−1.18, −0.53)** **<0.001**	**−0.89 (−1.20, −0.58)** **<0.001**	**−1.01 (−1.32, −0.71)** **<0.001**	
Rate ratio vs. PBO, (95% CI) p-value[e]	**0.30 (0.17, 0.50)**	**0.27 (0.16, 0.46)** **<0.001**	**0.17 (0.08, 0.33)** **<0.001**	
% reduction vs. PBO, (95% CI) [f]	**-70.5 (-82.7, -49.7)**	**-73.3 (-84.3, -54.5)**	**-83.4 (-91.6, -67.1)**	

Source: Table 2, p2114 of Banerji et al (2018)2, Table 14.2.5.3, p372 of the HELP CSR. **Results in bold are statistically significant.**
Blue shading indicates data presented in the previous submission and considered by PBAC previously.
CI = confidence interval; PBO = placebo; Q2W = every 2 weeks; Q4W = every 4 weeks; SC = subcutaneous; SD = standard deviation.
[a] All patients received injections every 2 weeks, with those in the every-4-week groups receiving placebo in between active treatments
[b] Attack rates are model-based mean attacks per month, defined as 4 weeks.
[c] Results are from a Poisson regression model accounting for over dispersion; treatment group and normalized baseline attack rate were fixed effects. The logarithm of time (days) each patient was observed during the treatment period was an offset variable. All P values (Wald test) reported vs placebo
[d] Estimated from a nonlinear function of the model parameters. All P values (Wald test) reported vs placebo
[e] p-value adjusted for multiple testing
[f] % change in mean rate corresponds to 100% × (Estimated mean rate ratio – 1) – Rounded. A negative sign for % reduction versus PBO implies a reduction in mean attack rate favouring lanadelumab over placebo.

[2] Banerji A, Riedl MA, Bernstein JA, Cicardi M, Longhurst HJ, Zuraw BL, et al. Effect of Lanadelumab Compared with Placebo on Prevention of Hereditary Angioedema Attacks: A Randomized Clinical Trial. *JAMA* 2018;320(20):2108-21

6.8 The results for the primary outcome are also presented in the figure below.

Figure 1: Investigator-confirmed HAE attacks during the treatment period by treatment group (ITT population, Poisson regression, Day 0 to Day 182)



Source: Figure 4, HELP trial CSR
HAE = hereditary angioedema; ITT = intent-to-treat

6.9 For Day 0 to Day 182 (26 weeks of follow-up), the lanadelumab 300 mg Q4W and 300 mg Q2W treatment regimens resulted in statistically significant reductions in the mean HAE attack rate (per month) versus the placebo treatment arm (73.3% and 86.9% reductions, respectively; p<0.001). The PBAC noted that the lanadelumab 150 mg Q4W regimen also resulted in a statistically significant reduction in the mean HAE attack rate versus placebo (75.6% reduction; p<0.001).

6.10 Statistically significant reductions associated with the lanadelumab 300 mg Q4W and 300 mg Q2W treatment regimens versus placebo (Day 0 to Day 182) were also observed for the endpoints of:

- Attacks/month requiring rescue or acute treatment (74.2% and 87.3% reductions, respectively); and
- Moderate or severe attacks/month (73.3% and 83.4% reductions, respectively).

6.11 The extent of clinical benefit associated with lanadelumab over placebo observed in the HELP trial, although significant, was associated with wide confidence intervals, primarily due to the small size of the study.

6.12 The evaluation considered that long term comparative efficacy is also lacking (given the 26-week HELP study period), considering that therapy is likely to be on-going in many patients. The Pre-Sub-Committee Response (PSCR) provided data from the

extension phase of the HELP trial in which all patients were offered the opportunity to roll-over into an extension study. The PSCR stated that at the time of submission, the collective total subject-time for the 109 rollover patients was 714 months. In the extension study, the lanadelumab treatment effect was maintained with the mean HAE attack rate in lanadelumab-treated patients (300mg Q2W) decreasing from 0.26 attacks per month during the randomised period to 0.18 attacks per month during the extension study.

6.13 The TGA evaluation report noted that the limitations regarding the efficacy results relate to the small number of patients included in the HELP trial and the inherent variability and unpredictability in HAE attack pattern and frequency. This was demonstrated by 1) some responders in the HELP trial who subsequently became non-responders (N = 3) in the HELP extension phase due to "significant life-changing stress events", and 2) the substantial reduction in HAE attack rate per month in the placebo arm of HELP (median of 3.00 attacks/month during the run-in period to a median of 1.69 attacks/month in the treatment period). This inherent variability in HAE attack rates and the potential for unpredictable changes in life events to trigger attacks raises concerns regarding the results of the main efficacy study in the context of the small study size, and that the study results may be confounded by this variability and reflect changes in life events rather than the effects of lanadelumab.

6.14 The resubmission stated that patients treated with lanadelumab experienced a significantly greater reduction (i.e., improvement) in the Angioedema Quality of Life (AE-QoL) total score and all domain (functioning, fatigue/mood, fear/shame, and nutrition) scores, relative to the placebo arm ($p < 0.04$ for the AE-QoL total and all domain scores). These analyses were conducted post hoc and no apparent adjustment for multiplicity testing was conducted. There were no significant changes in EQ-5D results.

6.15 The HELP trial did not permit (by design) routine prophylaxis (short or long term) during the randomised treatment phase. The resubmission stated that danazol (AZOL®) was being withdrawn from the market by the supplier Mylan[3], however it is noted that danazol is still listed on the PBS and resupply may occur, with multiple danazol brands potentially available from other suppliers[4]. The comparative benefit in reduction of attack rates favouring lanadelumab observed in HELP may be an overestimate if SOC in clinical practice constitutes some form of routine prophylaxis, including use of oral prophylaxis (or SC C1-INH in patients with severe HAE).

6.16 The PSCR stated 'it is expected that patients not achieving adequate efficacy and/or experiencing unacceptable toxicities with oral prophylaxis would switch to lanadelumab as the sole prophylactic agent. The ESC agreed that lanadelumab was unlikely to be used in combination with oral prophylaxis in clinical practice, but noted

[3] https://apps.tga.gov.au/Prod/msi/Search/Details/danazol

[4] https://allergy.org.au/about-ascia/info-updates/product-supply-update-danazol

that the incremental benefit may be reduced if the comparison was SOC including oral prophylaxis versus lanadelumab. The ESC agreed with the PSCR that 'if danazol is not available on the PBS, the limited use of oral prophylaxis in the trial is consistent with current clinical practice'.

6.17 Further applicability concerns included the baseline attack frequency and period of assessment in the HELP trial compared with Australian clinical practice. The required baseline attack rate threshold for enrolment into HELP (equivalent of ≥ 1 investigator-confirmed HAE attack per month), and corresponding monitoring period (8 weeks run in) were both lower and shorter, respectively, compared those proposed in the requested restriction (threshold of ≥ 12 treated acute attacks per 6-month (equivalent of ≥ 2 treated attacks per month) with a proposed monitoring period of "within" 6 months). The run in monitoring period of up to 8 weeks in HELP may not have been sufficiently long to capture a stable baseline attack rate distribution in the enrolled patients. Data on HAE frequency/severity in HAE patients from Australian clinical practice were limited.

6.18 The reduction of lanadelumab 300 mg dose frequency, from Q2W to Q4W for patients who are "stably" attack free, was not addressed in the HELP trial, in which lanadelumab treatment arms were fixed dose regimens. The ESC noted that the HELP extension study only investigated the Q2W dose, but there is an ongoing open-label study in Japan assessing the use of lanadelumab Q2W for 26 weeks followed by a 26-week treatment period in which patients could remain on the Q2W regimen or receive the Q4W regimen.[5] The ESC considered that clinical immunologists are experienced at down-titrating medications and would likely try to use the lowest effective dose once a patient's condition is stabilised. The ESC further noted that there may be a patient preference, among some patients, for Q4W rather than Q2W dosing. The ESC considered it was unclear what proportion of patients in clinical practice would transition to the Q4W dose, but considered that the resubmission's assumption that [redacted]% of patients would down-titrate was likely to overestimate the use of the Q4W regimen in clinical practice.

Comparative harms

6.19 Safety data from the HELP trial have not changed from the previous submission. A summary of key adverse events (AEs) in HELP is provided below.

[5] https://clinicaltrials.gov/ct2/show/NCT04180163?term=lanadelumab&cntry=JP&draw=2&rank=1

Table 6: Summary of key adverse events in the HELP trial

AE	Lanadelumab				Placebo N=41
	150 mg Q4W N=28	300 mg Q4W N=29	300 mg Q2W N=27	Total N=84	
	n (%)	n (%)	n (%)	n (%)	n (%)
Any TEAE	25 (89.3%)	25 (86.2%)	26 (96.3%)	76 (90.5%)	31 (75.6%)
Any treatment-related TEAE	17 (60.7%)	14 (48.3%)	19 (70.4%)	50 (59.5%)	14 (34.1%)
Any SAE	0 (0%)	3 (10.3%)	1 (3.7%)	4 (4.8%)	0 (0%)
Any treatment-related SAE	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Any severe (grade 3/4) TEAE	2 (7.1%)	4 (13.8%)	2 (7.4%)	8 (9.5%)	4 (9.8%)
Any treatment-related severe TEAE	0 (0%)	1 (3.4%)	0 (0%)	1 (1.2%)	1 (2.4%)
Any investigator reported AESI	1 (3.6%)	1 (3.4%)	3 (11.1%)	5 (6.0%)	0 (0%)
Death	0 (0 %)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Discontinuation due to TEAE	0 (0%)	1 (3.4%)	0 (0%)	1 (1.2%)	1 (2.4%)

Source: Table 36, p64 of the resubmission.
AE = adverse event; AESI = adverse event of special interest; Q2W = every 2 weeks; Q4W = every 4 weeks; SAE = serious adverse event; TEAE = treatment emergent adverse event.
Blue shaded results were those considered by PBAC previously.

6.20 Treatment-related AEs reported in ≥ 5% of patients receiving lanadelumab (% of lanadelumab treated patients vs % of placebo treated patients) were: injection site pain (41.7% vs 26.8%), headache (7.1% vs 2.4%), injection site erythema (9.5% vs 2.4%) and injection site bruising (6.0% vs 0%).

6.21 The TGA evaluator concluded that lanadelumab appears to be well tolerated but noted that only a small number of patients have been exposed and only for relatively short periods of time, although it is proposed for long-term use.

Benefits/harms

6.22 A summary of the comparative benefits and harms for lanadelumab versus placebo is presented in the table below.

Table 7: Summary of comparative benefits and harms for lanadelumab and placebo

Benefit							
	Lanadelumab 300mg Q2W			**PBO**			**Mean difference: Lanadelumab vs PBO (95% CI)**
	N	**Mean**	**95% CI**	**N**	**Mean**	**95% CI**	
Attack rate per month during treatment period*	27	0.26	0.15, 0.46	41	1.97	1.64, 2.36	**-1.71 (-2.09, -1.33)**

Harms						
	Lanadelumab n/N**	**PBO n/N**	**RR (95% CI)**	**Event rate/100 patients***		**RD (95% CI)**
				Lanadelumab	**PBO**	
Any treatment-related TEAE	50/84	14/41	1.74 (1.10, 2.76)	59.5	34.1	**0.25 (0.07, 0.43)**
Any SAE	4/84	0/41	NE	4.8	0	0.05 (0.00, 0.09)

Source: Table 2, p2114 of Banerji et al (2018)[6], Table 14.2.5.3, p372 of the HELP CSR, and Table 30, p50 of the resubmission.
CI = confidence interval; NE = not evaluable; PBO = placebo; Q2W =every 2 weeks; RD = risk difference; RR = risk ratio, TEAE = treatment emergent adverse event; SAE = serious adverse event.
* 26 weeks of treatment period
**all patients treated with lanadelumab, regardless of dose regimens.

6.23 On the basis of direct evidence presented by the resubmission, for patients treated with lanadelumab 300 mg Q2W in comparison with placebo over a 26 week treatment period, they will experience, on average, 1.71 fewer HAE attacks per month. This corresponded to an approximate 87% reduction in the mean attack rate compared with placebo.

6.24 For every 100 patients treated with lanadelumab in comparison with placebo over a 26 week treatment period:

- Approximately 25 additional patients would experience a treatment related treatment-emergent adverse event;
- Approximately 5 additional patients would experience a serious adverse event.

Clinical claim

6.25 The resubmission described lanadelumab as superior in terms of effectiveness and inferior in terms of safety compared to placebo.

6.26 The therapeutic conclusion presented in the resubmission, between lanadelumab + ODT, and placebo (no routine prophylaxis) + ODT, was adequately supported by the evidence from the HELP trial. However, the evaluation and the ESC considered that the evidence should be interpreted with caution given the following issues:

- The applicability of the clinical benefit from the key HELP trial, associated with lanadelumab versus placebo, to Australian clinical practice remains potentially uncertain. Around half (56%) of the patients in the HELP trial had used a form of

[6] Banerji A, Riedl MA, Bernstein JA, Cicardi M, Longhurst HJ, Zuraw BL, et al. Effect of Lanadelumab Compared with Placebo on Prevention of Hereditary Angioedema Attacks: A Randomized Clinical Trial. JAMA - Journal of the American Medical Association. 2018;320(20):2108-21.

long-term prophylaxis within three months prior to screening (the majority of prophylaxis was with IV C1-INH). Should routine prophylaxis (oral prophylaxis with danazol/tranexamic acid, or with C1-INH in NBA qualifying patients) remain a main part of the clinical management of HAE in Australian SOC, the comparative effectiveness result from HELP may be an overestimate of clinical practice given a selection bias for more treatment experienced patients with the proposed restriction.

- The evaluation considered that the extent of benefit in terms of a reduction of attack rates, associated with lanadelumab 300 mg (Q2W or Q4W regimens) versus placebo, was imprecise due to the small number of patients as reflected by the wide 95% confidence intervals. The ESC considered that the incremental benefit of lanadelumab observed in the HELP trial was clinically meaningful even at the upper limit of the 95% CI, with a reduction in the mean HAE attack rate per month of 86.9% (95% CI: 92.8%, 76.2%) in the Q2W arm versus placebo.
- The evaluation considered that long term comparative efficacy was lacking (given the 26-week HELP study period), considering that therapy is likely to be on-going in many patients. However, the ESC noted that data from the extension study provided in the PSCR, while non-comparative and based on the Q2W regimen only, indicated that the treatment effect of lanadelumab appeared to be maintained over time.

6.27 The PBAC considered that the claim of superior comparative effectiveness was reasonable, but considered there was residual uncertainty in the magnitude of benefit due to the small patient numbers in the trial and potential applicability issues.

6.28 The PBAC considered that the claim of inferior comparative safety was reasonable, and that, based on the evidence available, lanadelumab appears to be well tolerated.

Economic analysis

6.29 The resubmission presented a stepped economic evaluation based on the direct randomised trial HELP and implementing a modelled evaluation. The economic evaluation only assessed the cost-effectiveness of lanadelumab compared with SOC. The evaluation considered that, for patients who experience 8 or more attacks per month, prophylactic C1-INH may have been a more appropriate comparator, especially given that the availability of the subcutaneous injection of C1-INH is likely to increase uptake in eligible patients. However, it was acknowledged that there is a lack of comparative evidence in terms of lanadelumab versus SC C1-INH, and that these patients would only be expected to represent a small proportion of the proposed PBS population for lanadelumab. The previous submission presented a cost-minimisation analysis of lanadelumab compared with IV C1-INH, based on an indirect comparison of these two treatments.

6.30 The model structure, key inputs and rationale are summarised below.

Table 8: Summary of model structure, key inputs and rationale

Component	Description
Treatment	Lanadelumab versus SOC
Population	Patients experiencing ≥ 24 treated attacks over 12 months
Type of analysis	Cost-utility analysis
Time horizon	1 year
Outcomes	HAE attacks, quality-adjusted life years
Utilities	'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
Methods used to generate results	Cohort expected value
Health-related quality of life	'Between-attack' utility reflecting frequency, average severity and duration of HAE attacks was applied. An 'in-attack' disutility was also applied.
Software package	Excel 2016

Source: Table 48, p94 of the resubmission
HAE = hereditary angioedema; SOC = standard of care.

6.31 The model in the resubmission was a cohort expected value analysis with a one-year time horizon. While lanadelumab is intended to be used for ongoing prophylaxis of HAE attacks, the extrapolation of outcomes from a 6-month comparative trial over an extended period would have added considerably to the existing uncertainty regarding the validity of the outcome of the model.

6.32 The steps in the economic evaluation, as presented in the resubmission, are summarised below.

Table 9: Steps in the economic evaluation

Step	Description
Step 1	Trial-based analysis: cost per investigator-confirmed HAE attack avoided within trial period (182 days) (primary outcome of HELP), 13 doses of prophylaxis in the lanadelumab arm (300 mg Q2W).
Step 2	Trial-based analysis: as above but using the outcome of cost per investigator-confirmed HAE attack requiring acute treatment avoided.
Step 3	Economic model: Extrapolation to 1 year, assuming a baseline attack rate of 24 treated HAE attacks per year. Patients in the lanadelumab arm assumed to receive 26 doses of prophylaxis per year.
Step 4	Treated attacks avoided transformed to QALYs gained, and assuming patients in the lanadelumab arm receive [redacted] doses of prophylaxis per year (based on the assumption that [redacted]% of patients receive the reduced dose of 300 mg Q4W).
Step 5	Incorporating cost of treating acute HAE attacks
Step 6	Weighted ICER calculated by applying baseline treated HAE attack frequency distribution sourced from PBS data for use of icatibant.

Source: Table 65, p110 of the resubmission.
DUSC = Drug Utilisation Subcommittee; HAE = hereditary angioedema; ICER = incremental cost-effectiveness ratio; Q2W = every 2 weeks; Q4W = every 4 weeks; QALY = quality-adjusted life-year.

6.33 The resubmission used the following approach:

- An analysis was undertaken by the DUSC Secretariat based on 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. Icatibant injections were used as a proxy for the number of treated HAE attacks per year. The resubmission identified 11 patients who had been dispensed ≥ 24 injections of icatibant over a 12-month period, who were considered to be eligible for lanadelumab. The baseline frequency of HAE attacks in the SOC arm of the model was based on these 11 patients.
- The distribution of HAE attacks in the lanadelumab arm was then estimated by applying the relative risk reduction from the lanadelumab 300 mg Q2W arm of HELP to the number of attacks for each of the 11 patients.
- 'Between-attack' utilities were derived based on the frequency, severity and duration of attacks, with the severity and duration in each arm sourced from the HELP trial, and applied over the entire one-year time horizon. Disutilities for each severity of attack (mild, moderate or severe) were applied for the duration of each attack.
- The costs and quality-adjusted life-years (QALYs) accrued in each treatment arm were calculated for each baseline frequency of attacks reported for the 11 eligible patients identified from the PBS data.
- A weighted incremental cost-effectiveness ratio (ICER) was derived by calculating the mean incremental costs and the mean incremental QALYs for these 11 patients.

6.34 The distribution of baseline frequency of HAE attacks applied in the economic model was highly uncertain given that it was based on only 11 patients. In addition, 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.

6.35 As in the previous submission, in the economic evaluation, the cost of lanadelumab was based on the assumption that [redacted]% of patients would receive lanadelumab 300 mg Q2W and [redacted]% would receive the lower dose of 300 mg Q4W. However, the efficacy of lanadelumab in the model was based on data from the 300 mg Q2W treatment arm of HELP. The cost of lanadelumab should have been consistent with the dosing regimen on which the efficacy was based (300 mg Q2W). Furthermore, the PBAC previously considered that this assumption had resulted in an underestimate of the number of vials per patient (paragraph 7.13, lanadelumab PSD, July 2019 PBAC meeting). Therefore, the cost/patient/year for lanadelumab was likely to be an underestimate.

6.36 The utilities applied in the economic model were sourced from Nordenfelt 2014 and Nordenfelt 2017[7], both of which assessed health-related quality of life (HRQoL) in Swedish patients with HAE. Within the model, patient quality of life (QoL) was dependent upon attack frequency, severity and duration. The resubmission applied both 'between-attack' utilities and 'in-attack' disutilities in the economic model.

6.37 The 'between-attack' utility, which was a background utility value, varied between treatment arms, given the difference in frequency, severity and duration of the HAE attacks observed in the HELP trial.

6.38 To inform the 'between-attack' utility, data on the maximum attack severity and the mean duration of attacks for patients in the lanadelumab 300 mg Q2W and the placebo arms of the HELP trial were mapped to Angioedema Activity Scores (AAS). The average AAS score per attack was multiplied by the number of attacks per 28 days to generate an AAS28 score, and translated to utility values based on the values reported in Nordenfelt 2017.

6.39 The approach used in the resubmission may have overestimated the average AAS points per attack, given:

- The attack severity for all attacks was based on the maximum severity attack experienced by each patient throughout the entire 6 months of the trial, rather than the mean severity, i.e. every attack was assumed to be of the most severe intensity that the patient experienced during the trial;
- The AAS scores for attacks lasting >24-48 hours and >48 hours were estimated by, respectively, doubling and tripling the AAS scores for attacks >12-24 hour duration; this approach implicitly assumed that the severity of the attack was maintained over the extended time period.

6.40 As the average AAS score per attack was likely to be overestimated, the AAS28 scores were also likely to be overestimated. This is likely to have resulted in an overestimation of the utility decrement associated with each incremental increase in the number of attacks experienced per 28 days. As attacks were more frequent in the SOC arm, this would favour lanadelumab over SOC. The resubmission's approach to transforming treated attacks avoided to QALYs gained was complicated, involving multiple steps, each of which was subject to uncertainty in terms of validity and application. The 'between-attack' utilities were important drivers of the model results.

6.41 The table below shows that the utilities applied in the base case (Nordenfelt 2017) were based on a small sample size. For example, nine patients informed the utility value that was a key driver of the model (the utility value for a 'moderate' level of

[7] Nordenfelt P, Dawson S*, et al.* Quantifying the burden of disease and perceived health state in patients with hereditary angioedema in Sweden. *Allergy Asthma Proc*. 2014; 35 (2):185-90.
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.

AAS28 (0.64) was applied to 10 of the 11 patients in the SOC arm, while the utility value for 'zero' level of AAS28 (0.88) was applied to all patients in the lanadelumab arm).

Table 10: Utility value by level of AAS28 (Nordenfelt 2017)

	Level of AAS28			
	Zero	**Low**	**Moderate**	**High**
	n = 24	**n = 14**	**n = 9**	
Number of attacks/28 days to fall within each category (as applied in model)	0	1	≥2	
AAS28 score	0	1-24	25-75	76-420
EQ-5D-5L utility value, median (range)	0.88 (0.55-1.00)	0.80 (0.30-1.00)	0.64 (0.1-1.00)	No data[a]

Source: Table 54, p102 of the resubmission; Table 5, p452 Nordenfelt 2017.
AAS28 = Angioedema Activity Score for 28 consecutive days; EQ-5D-5L = EuroQol 5 dimensions 5 level.
a Only one patient in Nordenfelt 2017 had a high AAS28 level; this patient was omitted from the analysis because of skewing of the data.

6.42 Nordenfelt 2014 (which was used by the resubmission to estimate the in-attack disutility) reported an alternative approach to estimating between-attack utilities, based on a multiple regression model on EQ-5D scores, using data from 103 patients. This model estimated a utility decrement of 0.0043 per attack (and a mean EQ-5D 'between-attack' utility of 0.825, adjustments were also applied for patient age).

6.43 The PSCR argued that the between-attack utility using the Nordenfelt 2014 decrement underestimates the true nature of HAE attacks because it applies a single decrement per attack irrespective of the duration or severity of the attack. However, the ESC considered that it would be more reasonable to apply the utilities from Nordenfelt 2014 in the base case due to the larger sample size of the study and given that no significant difference in EQ-5D scores was observed between the placebo arm and any of the lanadelumab arms in the HELP trial.

6.44 The pre-PBAC response argued that Nordenfelt 2017: (1) uses a validated disease specific instrument (AAS28) which the pre-PBAC response stated better describes and differentiates the different aspects of HRQoL among patients with HAE than the EQ-5D instrument alone, which was used in the Nordenfelt 2014 study; (2) was less likely to be subject to recall bias as data were collected prospectively, in contrast to the Nordenfelt 2014 study; and (3) accounts for the severity and duration of attacks (which are not accounted for in Nordenfelt 2014).

6.45 However, the PBAC agreed with the ESC that the submission's approach to estimating between-attack utilities likely overestimated the utility decrement associated with each incremental increase in the number of treated attacks as the average AAS score per attack was likely to have been overestimated. Further, the PBAC acknowledged the ESC's advice the overall approach was complicated, involving multiple steps, each of which was subject to uncertainty in terms of validity and application (as outlined in Paragraphs 6.39 to 6.40).

6.46 'In-attack' disutility values were obtained from Nordenfelt 2014. The model was less sensitive to the 'in-attack' disutility due to the short durations to which the disutility applied.

6.47 The key drivers of the model are summarised below.

Table 11: Key drivers of the model

Description	Method/Value	Impact
The mean cost/patient/year for lanadelumab	Assuming that [redacted]% of patients receive the reduced dose of 300 mg Q4W	High, favours lanadelumab
The distribution of baseline attack frequency	Baseline attack frequencies of 11 patients who had been dispensed ≥ 24 injections of icatibant over a 12-month period, as reported in PBS data.	High
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, 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 weighted RRR for the Q2W arm ([redacted]%) and the Q4W arm ([redacted]%), consistent with the costings for lanadelumab.	High, favours lanadelumab

Source: Table 65, p109 of the resubmission; Excel workbook 'LANA_resubmission_HAE_Sec3_CUA
HAE = hereditary angioedema; Q4W = every 4 weeks; RRR = relative risk reduction; SOC = standard of care.

6.48 The results of the stepped economic evaluation are summarised below.

Table 12: Results of the stepped economic evaluation

	Costs			Outcomes			ICER
	LANA	SOC	Inc	LANA	SOC	Inc	
1) HELP trial-based analysis: Cost per investigator-confirmed HAE attack avoided at 182 days (13 doses)	$[redacted]	$0.00	$[redacted]	12.786	1.672	11.113	less than $15,000 per HAE attack avoided
2) As above but with HAE attack "requiring acute treatment" endpoint	$[redacted]	$0.00	$[redacted]	10.641	1.392	9.249	$15,000 - $45,000 per HAE attack requiring treatment avoided
3 Economic model: 24-attacks a year baseline rate, cost per HAE attack requiring treatment avoided at 1-year (26-doses)	$[redacted]	$0.00	$[redacted]	24.000	3.048	20.952	less than $15,000 per HAE attack requiring treatment avoided
4a) As above, HAE attacks transformed to QALYs gained (26 doses)[a]	$[redacted]	$0.00	$[redacted]	[redacted]	[redacted]	[redacted]	more than $200,000/QALY
4b) As for 4a, assuming [redacted] doses[a]	$[redacted][b]	$0.00	$[redacted]	[redacted]	[redacted]	[redacted]	more than $200,000 /QALY more than $200,000/QALY [b]
5) As above, including costs of treating acute HAE attacks	$[redacted]	$80,817	$[redacted]	[redacted]	[redacted]	[redacted]	more than $200,000/QALY more than $200,000/QALY [b]
6) As above, weighted using the mean incremental cost and incremental QALY for the 11 baseline attack frequencies reported by the 11 patients from PBS data (base case)	$[redacted]	$185,205	$[redacted]	[redacted]	[redacted]	[redacted]	$45,000 - $75,000

Source: Table 65, p109 of the resubmission; Excel workbook 'LANA_resubmission_HAE_Sec3_CUA

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

[a] For the purposes of the evaluation, this was performed in 2 steps: firstly, transforming attacks to QALYs (26 doses of lanadelumab) and, secondly, applying the weighted mean dose of [redacted] doses per patient.

[b] In Section 3.8.1, p107 and the Section 3 Excel workbook the cost/patient/ year for lanadelumab ([redacted] doses) was reported as $[redacted].

6.49 The following steps had a considerable impact on the model results:

- The transformation of treated attacks avoided to QALYs gained;
- The assumption that only [redacted]% of patients would require a dose of lanadelumab 300 mg Q2W (26 doses per year), with the remaining [redacted]% of patients receiving lanadelumab 300 mg Q4W (13 doses per year);
- The inclusion of the costs associated with treatment of acute HAE attacks; and
- The application of the weighted frequency of baseline attacks based on the PBS data for icatibant (steps 3-5 assumed 24 attacks per year; distribution derived using data provided by the DUSC Secretariat: mean 55 attacks per year).

6.50 The results of key sensitivity analyses presented in the resubmission and performed during the evaluation and by ESC are summarised below.

Table 13: Results of key sensitivity analyses

Analyses		Incremental cost	Incremental QALY	ICER $/QALY gained
Base case		$ [redacted]	[redacted]	$ [redacted]
Univariate sensitivity analyses				
1.	Excluding the patient with 136 attacks per year [a]	$ [redacted]	[redacted]	$ [redacted]
2.	Cost of lanadelumab (Base case [redacted]% Q2W, [redacted]% Q4W; mean [redacted] doses/patient/year)			
	a) 100% Q2W (26 doses/year)	$ [redacted]	[redacted]	$ [redacted]
	b) 50% Q2W, 50% Q4W (mean 19.5 doses/year)	$ [redacted]	[redacted]	$ [redacted]
	c) 100% Q4W (13 doses/year)	-$ [redacted]	[redacted]	Dominant
3.	LANA efficacy (Base case: 100% Q2W RRR 0.873)			
	a) Weighted [redacted]%:[redacted]% Q2W:Q4W ([redacted])	$ [redacted]	[redacted]	$ [redacted]
	b) Weighted 50:50% Q2W:Q4W (0.807)	$ [redacted]	[redacted]	$ [redacted]
	c) 100% Q4W (0.742)	$ [redacted]	[redacted]	$ [redacted]
4.	'Between-attack' utility values (Base case: no attacks 0.88; 1 attack/28 days 0.80; ≥2 attacks/28 days 0.64)			
	Nordenfelt 2014 (0.825 for 0 attacks, decreasing by 0.0043 for each additional attack per 28 days) [b]	$ [redacted]	0.0934	$ [redacted]
Multivariate sensitivity analyses				
5.	**2b+3b**: Cost and efficacy of lanadelumab based on 50% Q2W; 50% Q4W (RRR: 0.807 and mean 19.5 doses/year)	$ [redacted]	0.2633	$ [redacted]
5 + 4: Cost and efficacy 50% Q2W: 50% Q4W + Nordenfelt 2014 utilities		$ [redacted]	0.0755	$ [redacted]
5 + 1 Cost and efficacy 50% Q2W: 50% Q4W + exclude 136 attacks/yr		$ [redacted]	0.2713	$ [redacted]
5 + 1 + 4 Cost and efficacy 50% Q2W: 50% Q4W + exclude 136 attacks/yr + Nordenfelt 2014 utilities		$ [redacted]	0.0613	$ [redacted]
1 + 3a + 4: Exclude 136 attacks/yr + RRR 0.77 + Nordenfelt 2014 utilities		$ [redacted]	[redacted]	$ [redacted]

Source: Table 69, p113 of the resubmission; Excel workbook "LANA_REsubmisison_HAE_Sec3_CUA"

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

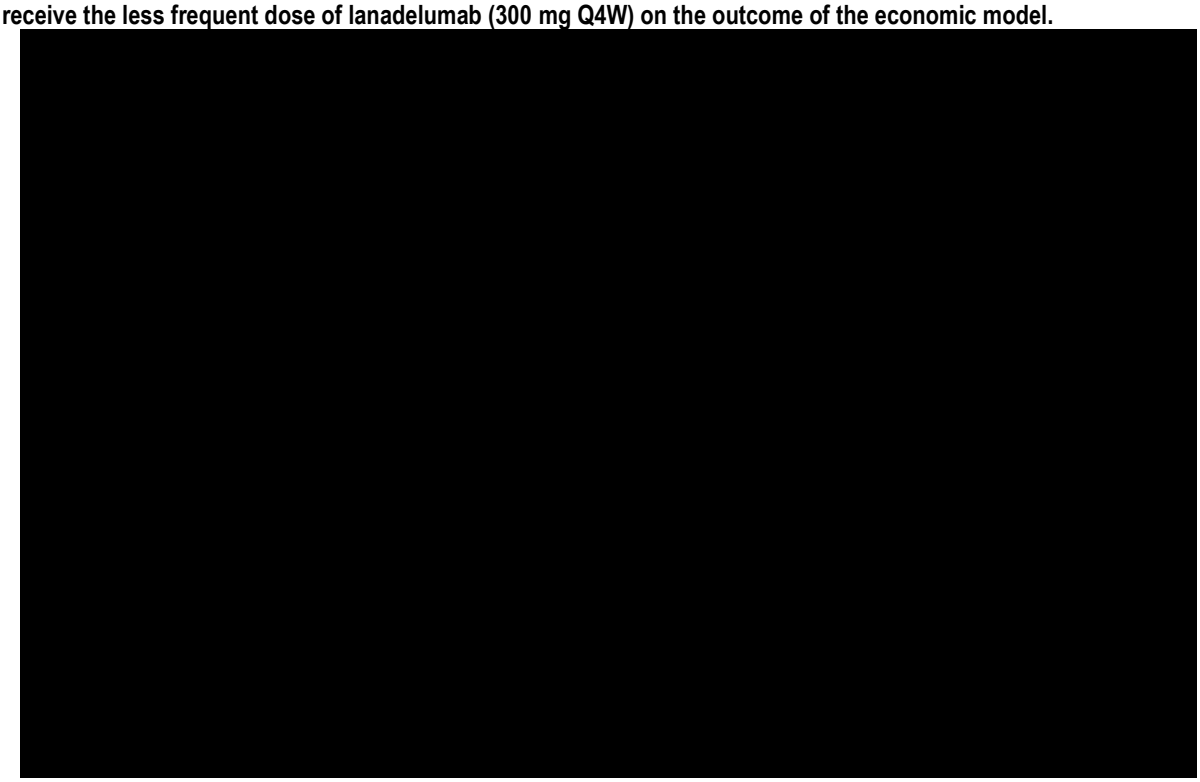
[a] As this patient experienced, on average, more than 8 attacks per month, routine prophylaxis with C1-INH may be a more appropriate comparator than SOC in this patient.

[b] 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.

6.51 The redacted table shows ICERs in the range of $ 45,000/QALY - $75,000/QALY to more than $200,000/QALY.As discussed above, when determining the 'between-attack' utility based on the frequency, severity and duration of attacks, the resubmission may have overestimated the utility decrement associated with each incremental increase in the number of treated attacks experienced per 28 days. The sensitivity analysis performed during the evaluation, using an alternative 'between-attack' utility (0.825 for 0 attacks, with a decrement of 0.0043 for each additional attack per 28 days, based on results from Nordenfelt 2014) resulted in an ICER of $105,000/QALY - $200,000/QALY gained. The ESC considered that the Nordenfelt 2014 utilities were more appropriate to use in the base case.

6.52 Figure 2 illustrates the impact of the baseline frequency of treated HAE attacks on the outcome of the economic model, firstly for the base case, in which [redacted]% of patients were assumed to receive the less frequent dose of lanadelumab (300 mg Q4W), and secondly assuming that all patients receive lanadelumab 300 mg Q2W.

Figure 2: Impact of the baseline frequency of treated HAE attacks and the proportion of patients assumed to receive the less frequent dose of lanadelumab (300 mg Q4W) on the outcome of the economic model.



Source: Constructed during the evaluation from data in the Excel workbook "LANA_REsubmisison_HAE_Sec3_CUA"
ICER = incremental cost-effectiveness ratio; HAE = hereditary angioedema; Q2W = every 2 weeks; Q4W = every 4 weeks; QALY = quality-adjusted life-year
Note: the mean number of attacks requiring acute treatment in the placebo arm of HELP was 1.64 per 4 weeks (approximately 21 per year).

6.53 The cost-effectiveness of lanadelumab for the prophylaxis of HAE attacks was highly sensitive to the baseline HAE attack rate. As discussed above, the distribution of baseline attack rates was a major source of uncertainty in the economic model. The estimated ICER in patients experiencing a baseline treated attack rate of 24 treated attacks per year (an approximation for the threshold PBS eligibility attack rate of 12 treated attacks in 6 months) was more than $200,000/QALY gained. The ICER fell below $75,000/QALY – $105,000/QALY at a baseline attack frequency of 50 treated attacks per year, with lanadelumab dominating at baseline rates of ≥ 60 per year. Given that C1-INH may be a more appropriate comparator than placebo in patients experiencing ≥ 8 treated attacks per month (96 per year), the evaluation considered it may have been appropriate to exclude these patients from the cost-effectiveness analysis versus placebo. When the patient from the PBS data who received 136 injections of icatibant over 12 months was excluded from the analysis, the ICER increased to $105,000/QALY - $200,000/QALY gained.

6.54 The ESC considered that variability in HAE attack rates has a major impact on the results of the economic model, and noted that there is a large degree of variability in HAE attack rates between and within patients as evidenced by the differences in baseline HAE attack rates between arms in the HELP trial (ranging from 4.02 attacks per month in the placebo arm to 3.52 in the Q2W arm). The ESC considered this added to the uncertainty in the model.

6.55 The proportion of patients who were assumed to receive the less frequent dose of lanadelumab (300 mg Q4W) also had a considerable impact on the result of the economic model. If all patients were assumed to receive lanadelumab 300 mg Q2W, consistent with the dose at which the efficacy results applied in the model were observed, the ICER increased to more than $200,000/QALY gained. On the other hand, the ESC noted that the ICER is dominant if all patients are treated with the Q4W regimen, noting that the TGA Product Information recommends that the Q4W dose may be considered for patients who are 'stably attack free on treatment'.

6.56 The ESC considered that, while clinical immunologists would generally try to use the lowest effective dose once the condition is stabilised, it was unlikely that the proportion of patients transitioning to the Q4W dosing regimen would be as high as the [redacted]% assumed in the resubmission. The ESC considered that it was unclear what proportion of patients would transition to the Q4W dose in clinical practice, but noted that a multivariate sensitivity analysis in which costs and efficacy were both adjusted to account for 50% of patients remaining on the Q2W dose (and 50% transitioning to Q4W) resulted in an ICER of more than $200,000/QALY.

Drug cost/patient/year

Table 14: Drug cost per patient per year for lanadelumab (effective price)

	Trial dose[a]	Model	Financial estimates
Mean dose	300 mg Q2W[a]	23% 300 mg Q2W [redacted]% 300 mg Q4W	[redacted]% 300 mg Q2W [redacted]% 300 mg Q4W
Mean number of doses/patient/year	26.0[a]	[redacted]	[redacted]
Cost/patient/month	$[redacted][b]	$[redacted][b]	$[redacted][b]
Cost/patient/year	$[redacted][b]	$[redacted][b]	$[redacted][b]

Source: Table 14, p21 and Section 3.8.1 p107 of the submission.

Q2W = every 2 weeks; Q4W = every 4 weeks

[a] In both Sections 3 and 4 of the resubmission, the efficacy of lanadelumab was based on the results for the lanadelumab 300 mg Q2W arm of the HELP trial.

[b] The dispensed price use in the resubmission assumed that patients only received one 300 mg vial of lanadelumab per script. The requested maximum quantity was two vials. Thus the cost/patient/year was updated during evaluation based on the DPMQ, i.e. assuming that patients receive 2 x 300 mg vials of lanadelumab per script.

6.57 The estimated cost of lanadelumab per patient per year was $[redacted]. This was based on a proposed effective dispensed price of $[redacted] for two 300 mg vials, assuming [redacted]% of patients receive 300 mg Q4W (13 vials per year) and [redacted]% receive 300 mg Q2W (26 vials per year) (weighted mean of [redacted] vials per patient per year).

6.58 This compared to an estimated cost/patient/year of $[redacted] in the previous submission. This was based on a proposed DPMQ 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

6.59 This resubmission was not considered by DUSC.

6.60 The resubmission estimated the use of lanadelumab in two patient populations, consistent with the two initial treatment restrictions outlined above:

- Patients who are not receiving routine prophylaxis with C1-INH but who qualify for lanadelumab under the proposed 'initial treatment – 1' restriction requiring patients to have experienced at least 12 treated acute attacks of HAE within a period of 6 months (referred to as population 1); and
- Patients receiving C1-INH as routine prophylaxis of HAE when lanadelumab is listed, who choose to switch to lanadelumab (referred to as population 2).

The resubmission did not establish the comparative effectiveness and safety of lanadelumab versus C1-INH, nor did it demonstrate that lanadelumab is cost-effective compared with C1-INH for prophylaxis of HAE attacks.

6.61 The key inputs in the financial estimates are outlined below.

Table 15: Key inputs for financial estimates

Parameter	Value applied and source	Comment
Population 1 (patients who experience ≥ 12 treated HAE attacks within 6 months)		
Prevalent HAE population	Prevalence of 1 in 50,000 based on literature review	While this source was reasonable, the prevalence of HAE in Australia is uncertain.
% patients eligible (≥ 12 treated attacks in 6 months)	[redacted]% Proportion of patients from PBS utilisation data for icatibant who received ≥24 injections of icatibant within 12 months of initial supply.	Icatibant utilisation data may not represent a reliable proxy for determining the number of treated HAE attacks. This was a major source of uncertainty in the financial estimates.
Initiating patients	[redacted] patients in Years 1-3, [redacted] patients in Years 4-6. Derived from the number of prevalent HAE patients (minus the number of patients receiving C1-INH prophylaxis), the % of patients eligible, and the uptake rate ([redacted]% in all years), with adjustment for discontinuations (15% in all years).	The resubmission inappropriately used prevalence data to estimate the number of patients initiating lanadelumab treatment each year.
Continuing patients	[redacted] in Year 2, increasing to [redacted] in Year 6. Patients not discontinuing treatment were carried over to the following year.	This considerable increase in continuing patients over Years 1-6 was due to the application of prevalence data to derive incident patients.
Total patient years of treatment	[redacted] in Year 1, increasing to [redacted] in Year 6. The number of patients each year in population 1 was multiplied by 92.5% to account for 15% discontinuation over each year (i.e. patients who discontinue assumed to receive 6 months of lanadelumab).	-
Population 2 (patients receiving C1-INH prophylaxis when lanadelumab is listed and who switch to lanadelumab)		
Total patients who would receive C1-INH prophylaxis in the absence of lanadelumab	[redacted] in Year 1, increasing to [redacted] in Year 6. Derived from NBA data on the utilization of IV C1-INH (vials dispensed). Assumed 75% of use was for routine prophylaxis. Number of patients derived assuming an average of 3.52 vials per dose and 104 doses per year (366 vials per patient per year).	This is likely to be an overestimate, given that only [redacted] patients were estimated to meet the initial treatment - 1 criteria (≥ 12 attacks within 6 months). The proportion of use of IV C1-INH that was for routine prophylaxis was a major source of uncertainty in the financial estimates.
Uptake rate	The resubmission assumed [redacted]% uptake in Year 1 and a further [redacted]% of those not switching in Year 1 assumed to switch in Year 2 (i.e. 15% x [redacted]% = [redacted]%), resulting in a cumulative uptake of [redacted]% in Years 2-6.	This uptake rate should have been applied to the number of patients who were receiving C1-INH prophylaxis when lanadelumab is first listed (i.e. [redacted] patients in Year 1 of listing), but in Years 2-6, the uptake rate of [redacted]% was applied to the total patients who would receive C1-INH prophylaxis in the absence of lanadelumab.
Number of vials		
Vials/patient/year	[redacted] The resubmission assumed that [redacted]% of patients receive 300 mg Q4W and [redacted]% received 300 mg Q2W.	The PBAC previously considered that this assumption had underestimated the number of vials per patient (Para 7.13, lanadelumab PSD, July 2019). This was a major source of uncertainty in the financial estimates.

Source: Sections 4.1 - 4.3 of the resubmission; Excel workbook "Electronic_Files_LANA_HAE_Sec4_BIM"
C1-INH = C1 esterase inhibitor; HAE = hereditary angioedema; IV = intravenous; NBA = National Blood Authority; PSD = Public Summary Document; Q2W = every 2 weeks; Q4W = every 4 weeks.

Population 1 (patients who experience ≥ 12 treated HAE attacks within 6 months)

6.62 The resubmission used an epidemiological approach to estimate the number of patients likely to initiate lanadelumab under the 'initial treatment - 1' criteria.

6.63 The resubmission estimated the number of eligible patients by estimating the number of 'at risk' patients, which comprised the prevalent HAE patient population (1 in 50,000 based on the ASCIA Position Paper and the literature more broadly) excluding patients who were already captured in Population 2 (those receiving C1-INH prophylaxis).

6.64 The resubmission then assumed that [redacted]% of 'at risk' patients[8] experienced at least 24 treated attacks in 12 months. This was based on the PBS utilisation data for icatibant. The limitations of using these data as a proxy for the number of eligible patients are discussed above. This step estimated the number of patients in the prevalent HAE population who would be eligible for lanadelumab, but the resubmission applied the estimates as incident patients. The evaluation considered this was not appropriate, as incident patients are already captured in the prevalent patient pool.

6.65 The resubmission assumed an uptake rate of [redacted]% each year, and applied the resulting number of patients as the number initiating treatment each year. A discontinuation rate of 15% each year was applied to determine the number of continuing patients in the following year. As a result of using the prevalence data as incidence data, the estimated number of patients likely to be treated inappropriately increased from less than 10,000 in Year 1 of listing ([redacted]% of the HAE population) to less than 10,000 patients in Year 6 (14.3% of the HAE population) (Table 15).

6.66 For the purposes of the evaluation, the financial estimates were recalculated, assuming that [redacted]% of the prevalent HAE patient population who were not receiving C1-INH prophylaxis would be eligible for lanadelumab under the 'initial treatment - 1' restriction. Given the considerable uncertainty in the estimated number of patients likely to be treated, discontinuations were not taken into consideration in the re-analysis.

6.67 The PSCR argued that the 'approach to estimating the number of patients is correct as a prevalent pool of patients is constantly "at risk" of becoming eligible over time'. The ESC agreed with the evaluation that the resubmission had effectively applied prevalence estimates as incidence rates, and considered that it was unlikely that an additional [redacted]% of the prevalent population will become eligible each year (noting that this would accumulate to [redacted]% of HAE patients being treated with lanadelumab by Year 6). However, the ESC considered that it was likely that the number of treated patients would increase over time, and that the evaluator's approach may have

[8] The 'at risk' patients comprised the prevalent HAE patient population excluding patients receiving C1-INH prophylaxis when lanadelumab is first listed and patients who commenced lanadelumab in previous years.

underestimated patient numbers as it did not account for new incident patients each year.

Population 2 (patients who would otherwise receive C1-INH prophylaxis)

6.68 The resubmission used a market share approach to estimate the number of patients likely to initiate lanadelumab under the 'initial treatment - 2' criteria.

6.69 The resubmission assumed that 75% of IV C1-INH use was for routine prophylaxis, and that each patient requires 366 x 500 IU vials per year[9]. As NBA utilisation data were not available by indication, the proportion of use of IV C1-INH that was for routine prophylaxis was a major source of uncertainty.

6.70 The resubmission noted that the MSAC Assessment Report for C1-INH estimated that between 4 and 8 patients would be eligible for routine prophylaxis each year, and added that this suggested over 30 patients would have initiated routine prophylaxis in the five years that IV C1-INH has been included on the NBA's NPL. The 4 to 8 patients each year in the MSAC Assessment Report for C1-INH was the total number of HAE patients expected to receive C1-INH each year, not the number of patients initiating treatment each year. The resubmission estimated that, in the absence of lanadelumab, less than 10,000 patients would receive routine prophylaxis with C1-INH. This represents approximately [redacted]% of the estimated total HAE patient population in Australia, yet, on the basis of the PBS utilisation data, which was collected prior to the listing of C1-INH on the NBA's NPL, the resubmission estimated that only [redacted]% of HAE patients would experience ≥ 24 HAE attacks per year. These assumptions are not internally consistent given that current C1-INH patients would only represent a small proportion of the proposed PBS population for lanadelumab.

6.71 The resubmission indicated that an uptake rate of [redacted]% was assumed in Year 1, with a further [redacted]% of those not switching in Year 1 assumed to switch in Year 2 (i.e. [redacted]% x [redacted]% = [redacted]%), with no further uptake in Years 3-6, resulting in a cumulative uptake of [redacted]%. In the calculations in the Excel workbook for Section 4, an uptake rate of [redacted]% was applied to the number of patients who, in the absence of lanadelumab, would receive C1-INH prophylaxis, resulting in further uptake in Years 3-6. The evaluation considered that the resubmission's approach resulted in a considerable overestimate of the number of patients switching from C1-INH prophylaxis to lanadelumab.

6.72 With the recent listing of the subcutaneous preparation of C1-INH on the NBA's NPL, uptake of lanadelumab in patients eligible for prophylactic treatment with C1-INH may be lower than assumed in the resubmission.

6.73 As in Section 3, the resubmission assumed that [redacted] % of patients would receive lanadelumab 300 mg Q4W and [redacted]% would receive 300 mg Q2W, with a weighted average of [redacted] vials per patient per year. The PBAC previously considered that this

[9] Based on the recommended dose of 20 IU/kg twice weekly and the weight distribution of the Australian population.

assumption had underestimated the number of vials per patient (paragraph 7.13, lanadelumab, PSD, July 2019 PBAC meeting).

6.74 The impact of lanadelumab on the reduced use of icatibant as ODT was calculated from the additional patients estimated to receive prophylaxis (either C1-INH or lanadelumab), 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 (referred to as the 'broader population' in the resubmission). The mean attack frequency applied in these estimates (33.6 treated attacks/year) was based on five patients from the PBS icatibant data who experienced ≥ 24 attacks but < 48 attacks per annum. While the use of an upper limit of 48 attacks per annum was conservative, given the small sample size and the unpredictability of acute attacks, any estimates derived from these data are subject to considerable uncertainty. The resubmission did not estimate the differential impact on the use of icatibant with lanadelumab versus C1-INH prophylaxis, inherently assuming that lanadelumab and C1-INH were equi-effective in reducing the number of HAE attacks requiring ODT.

6.75 The resubmission used a similar approach as that used for icatibant to estimate the savings to the Australian Government resulting from the reduction in the use of IV C1-INH for treatment of acute HAE attacks. The resubmission also estimated the savings resulting from patients switching from prophylaxis with IV C1-INH to lanadelumab, assuming that patients receive an average of 3.52 vials per dose and 104 doses per year (366 vials/patient/year). As discussed above, the evaluation considered that the number of patients likely to switch from C1-INH to lanadelumab was likely to be overestimated in the resubmission.

6.76 The estimated net financial implications to the PBS/RPBS and to the Australian Government health budget, based on the proposed effective price of lanadelumab, are summarised below.

Table 16: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients treated						
Population 1 Re-analysis[a]						
Population 2[b]						
Total patient years[c] Re-analysis[a]						
Number of vials dispensed[d] Re-analysis[a]						
Estimated financial implications of lanadelumab						
Cost to PBS/RPBS less copayments						
Population 1 Re-analysis[a]	$ $	$ $	$ $	$ $	$ $	$ $
Population 2	$	$	$	$	$	$
Total Re-analysis[a]	$ $	$ $	$ $	$ $	$ $	$ $
Estimated financial implications for icatibant ODT						
Cost to PBS/RPBS less copayments Re-analysis[a]	-$ -$	-$ -$	-$ -$	-$ -$	-$ -$	-$ -$
Net financial implications for the Australian Government health budget						
Net cost to PBS/RPBS Re-analysis[a]	$ $	$ $	$ $	$ $	$ $	$ $
Net cost to federal government for change in use of C1-INH[e] Re-analysis[a]	-$ -$	-$ -$	-$ -$	-$ -$	-$ -$	-$ -$
Net cost to Australian Government health budget Re-analysis[a]	$ $	$ $	$ $	$ -$	$ -$	$ -$
Previous submission July 2019						
Number of patients treated						
Net cost to PBS/RPBS	$	$	$	$	$	$

Source: Table 75 p122, Table 77 p127, Table 78 p127, Table 80 p128, Table 81 p128 and Table 82 p129 of the resubmission; Excel workbook "Electronic_Files_LANA_HAE_Sec4_BIM".

C1-INH = C1 esterase inhibitor; ODT = on-demand treatment.

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

[b] The resubmission's estimates of the number of patients in population 2 were considerably higher than the estimated number of patients likely to receive routine prophylaxis with C1-INH in the MSAC Assessment Report for IV C1-INH (approximately 8 per year).

[c] Applying 92.5% to the number of patients in population 1 to account for 15% discontinuation over each year (i.e. patients who discontinue assumed to receive 6 months of LANA)

[d] Assuming [redacted] vials per patient per year as estimated by the submission.

[e] Cost to the Australian Government for funding of 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%.

6.77 The total net cost to the PBS/RPBS of listing lanadelumab, including cost offsets resulting from reduced use of icatibant for the treatment of acute HAE attacks, was estimated to be $10 million to < $20 million million in Year 6, and a total of $60 - $100 million in the first 6 years of listing. This was a reduction from the original submission (estimated to be nearly $20 - $30 million in Year 6), despite increased patient numbers, primarily due to the reduced lanadelumab price.

6.78 The estimated net implications for government health budgets were highly uncertain. As stated above, the proportion of HAE patients likely to be treated with lanadelumab was potentially overestimated, while the assumption that [redacted]% of patients would receive lanadelumab at the lower dosage was likely to have underestimated the average cost of treatment per patient. In addition, the cost offsets resulting from reduced use of C1-INH for prophylaxis of HAE attacks were likely to be overestimated. There is also considerable potential for use outside the intended population, as there is no reliable way of confirming the frequency and severity of HAE attacks that a patient reports they are experiencing.

6.79 The resubmission stated that there were a limited number of patients currently receiving lanadelumab through a patient access program and proposed a grandfather provision to allow these patients to access PBS-subsidised treatment. The pre-PBAC response stated that, to date, less than 10,000 patients had received lanadelumab through the patient access program.

Financial Management – Risk Sharing Arrangements

6.80 The resubmission stated that the sponsor was willing to consider an appropriate risk sharing arrangement (RSA).

6.81 The PSCR stated 'in the current absence of any further utilisation data, it is proposed that an appropriate risk sharing arrangement could be used to help manage the uncertainty of lanadelumab utilisation used in the economic model'. However, no specific details were provided.

6.82 The ESC considered that an RSA may help manage the risk of lanadelumab not being cost-effective if fewer patients down-titrate to the Q4W regimen in practice than are assumed to down-titrate in the economic model. However, this would only reduce the risk to the Commonwealth if patient numbers are not overestimated (i.e. to ensure the caps are reached once the vials per patient exceed the threshold), and so any such RSA would need to be based on more reliable and conservative patient numbers.

6.83 An RSA may also help address the risk of patients continuing treatment beyond the intent of the continuation criteria.

6.84 The pre-PBAC response proposed a tiered RSA:

- Tier 1 was based on the patient estimates derived from the evaluation's re-analysis of population 1 (i.e. applying [redacted]% to the prevalent population each year, which the pre-PBAC response referred to as the 'minimum patients from SOC') plus population 2 (i.e. patients who would otherwise receive C1-INH prophylaxis).
- 'Above Tier 1' comprised new patients switching from SOC each year from Year 2 onwards (i.e. the difference between the submission's and the evaluation's analysis of population 1). The evaluation and the ESC considered that the population included in this tier should not have been included in the estimates as these were prevalent patients added as incident patients each year, although the

ESC acknowledged that the evaluation's approach (which the pre-PBAC response uses in Tier 1) may have underestimated patient numbers as it did not account for new incident patients each year. The pre-PBAC response stated 'Given the lack of data to further inform this scenario, it is proposed that the remaining uncertainty in patient numbers and cost-effectiveness is shared between [the sponsor] and the Commonwealth– that is any expenditure on additional patients above Tier 1 is rebated at [redacted]% to the agreed effective price'. The pre-PBAC response did not state whether a higher rebate level would apply for expenditure above this cap.

6.85 The RSA proposed in the pre-PBAC response is shown in the table below.

Table 17: RSA proposed in the pre-PBAC response

	Year 1	Year 2	Year 3	Year 4
Tier 1				
Patients who switch from SOC - prevalent in Year 1	[redacted]	[redacted]	[redacted]	[redacted]
Patients who switch from C1-INH	[redacted]	[redacted]	[redacted]	[redacted]
Cost to PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Above Tier 1				
Patients who switch from SOC - prevalent in Year 2 onwards	[redacted]	[redacted]	[redacted]	[redacted]
Cost with [redacted]% rebate	[redacted]	$[redacted]	$[redacted]	$[redacted]
Combined				
Total patients	[redacted]	[redacted]	[redacted]	[redacted]
Cost to PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Average cost per patient	$[redacted]	$[redacted]	$[redacted]	$[redacted]

Source: Table 1, p3 of the pre-PBAC response.
Note that the 92.5% continuation rate that was applied in the submission did not appear to have been applied in the estimates in the table above.

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

7 PBAC Outcome

7.1 The PBAC deferred its decision whether to recommend listing lanadelumab for routine (long term) prophylaxis of recurrent attacks of hereditary angioedema (HAE). The PBAC sought further information regarding the most appropriate patient population with regard to baseline HAE attack rate and continuation criteria. The PBAC considered that the ICER was high and uncertain and noted it was highly dependent on the baseline HAE attack rate. The PBAC also noted that the economic evaluation and financial estimates were sensitive to the dosage regimen assumed to be used in practice, while there was only a small difference in effectiveness between the dosage regimens used in the trial. The PBAC considered there is a high risk of usage outside the restriction, and an RSA with a [redacted]% rebate for use above the caps would be required.

7.2 The PBAC considered that there is a high clinical need for effective and tolerable prophylactic therapies for HAE, particularly in patients who have a high burden of

disease but who do not meet the eligibility requirements for C1-INH through the NBA. The PBAC acknowledged the consumer comments which were strongly supportive of listing lanadelumab, describing the lack of safe and effective alternative therapies in patients who do not meet the NBA criteria for C1-INH. The comments also described the convenience of lanadelumab compared with C1-INH (in terms of dosing frequency versus SC C1-INH, and ease of administration versus IV C1-INH) in patients with more severe disease.

7.3 The resubmission requested listing for patients who have experienced at least 12 treated acute attacks of HAE within a period of 6 months. In contrast to the previous submission, a separate clinical criterion was not proposed for patients who experienced a single life-threatening HAE attack within the previous 12 months. 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.

7.4 To be eligible for continuing treatment after 6 months, the resubmission proposed that a patient must have had a ≥ 50% reduction in the rate of HAE attacks per month, compared with baseline. The PBAC considered there were several issues with this approach 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.

7.5 The PBAC noted that the Australasian Society of Clinical Immunology and Allergy (ASCIA) 2020 HAE Position Paper states that danazol and tranexamic acid have historically been used for long term prophylaxis, however use is limited by side effects and relative lack of efficacy, respectively. The Position Paper and resubmission both noted that there are current supply issues with danazol in Australia. The Position Paper also notes that C1-INH (IV and SC) is available through the NBA for patients who experience the equivalent of eight or more acute HAE attacks per month, with the criteria based on MSAC advice that C1-INH would only be cost-effective in patients with this very high level of attack frequency.

7.6 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. While routine prophylaxis with C1-INH (IV or SC) 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.

7.7 The key clinical evidence presented was the HELP trial, which compared three dosage regimens of lanadelumab versus placebo (on-demand treatment was permitted in all arms). The HELP trial enrolled patients who had the equivalent of one or more HAE

attacks per month. At baseline, patients had a median of around three HAE attacks per month in the run-in period.

7.8 At 26 weeks of follow-up, all doses of lanadelumab resulted in statistically significant reductions in the mean HAE attack rate (per month) versus placebo (reductions of 75.6%, 73.3% and 86.9% were reported for the 150 mg Q4W, 300 mg Q4W and 300 mg Q2W dosage regimens, respectively; p<0.001). The PBAC considered this was a clinically meaningful benefit, but that the extent of benefit was uncertain due to the small number of enrolled patients (27 to 29 in each of the active arms) and the high level of variability between and within patients, along with the unpredictability in HAE attack pattern and frequency. The PBAC noted that routine prophylaxis was not permitted in the HELP trial and considered that the lanadelumab treatment effect may be lower in Australian clinical practice (than observed in the trial), if routine prophylaxis remains part of SOC in clinical practice.

7.9 The PBAC noted that there was little difference in outcomes between the three lanadelumab dosage regimens used in the trial (150mg Q4W, 300mg Q4W, 300mg Q2W), despite this range representing a four-fold difference in dosage. The PBAC further noted that the sponsor had not sought registration of a 150 mg formulation and that the TGA-approved Product Information specifies a starting dose of 300 mg Q2W, and that a dose reduction to 300 mg Q4W may be considered in patients who are stable and attack free on treatment. The PBAC noted the substantial difference in the cost per patient between the 300 mg Q4W and Q2W dose ($[redacted] versus $[redacted] per patient per year). The PBAC considered that, from a cost perspective, a dosage regimen with up-titration would be appropriate wherein patients commence on 300 mg Q4W and titrate up to 300 mg Q2W if HAE attacks continue. 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 300mg Q4W regimen.

7.10 The PBAC considered that the claim of inferior comparative safety was reasonable, and that, based on the evidence available, lanadelumab appears to be well tolerated.

7.11 The PBAC noted that the ICER was highly sensitive to the baseline HAE attack rate. The estimated ICER in patients who just meet the PBS eligibility threshold was more than $200,000/QALY gained (based on a baseline of 24 treated attacks per year to approximate the PBS eligibility of 12 treated attacks in 6 months), versus an ICER of $45,000/QALY – $75,000/QALY in the base case which estimated an average of 55 treated attacks per year. The PBAC noted there is a large difference between the number of attacks required for PBS eligibility and the point at which lanadelumab would likely become cost-effective.

7.12 The PBAC considered that the distribution of baseline frequency of HAE attacks applied in the economic model was highly uncertain given that it was based on: (1) data from only 11 patients; and (2) the number of injections of icatibant dispensed, which may not be a reliable proxy for the number of treated HAE attacks. The PBAC

considered that given the lack of reliable data to inform the likely average baseline number of HAE attacks, and the likely very high ICER in patients near the submission's proposed threshold for eligibility, further consultation would be required to ensure use is targeted to those patients with a higher clinical need in whom lanadelumab is likely to represent value-for-money.

7.13 The PBAC considered the base case of the economic evaluation, which resulted in an ICER of $45,000/QALY – $75,000/QALY, was uncertain and optimistic and that the ICER could plausibly be higher than $1 million/QALY. The PBAC considered that the key issues were the baseline attack rate applied in the model (as outlined above), uncertainty around the dosage regimen that would be likely used in clinical practice, and the likely optimistic between-attack utilities that were applied (at outlined in the 'Economic analysis' section). The PBAC noted the model was sensitive to the efficacy estimates and, although differences across the dosage regimens were relatively small, 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.

7.14 The PBAC considered that the financial estimates may have been overestimated as the submission effectively applied prevalence estimates as incidence estimates which meant that the estimated number of treated patients switching from SOC increased from less than 10,000 in Year 1 ([redacted]% of the HAE population) to less than 10,000 in Year 6 ([redacted]% of the HAE population). The PBAC agreed with the ESC that, while the number of treated patients would increase over time, the submission had overestimated patient numbers in Years 2 onwards.

7.15 The PBAC considered that there is a substantial risk of use of lanadelumab outside the restriction in patients experiencing fewer HAE attacks than permitted under the restriction, a population for whom lanadelumab is not likely to be cost-effective. The PBAC noted that use of C1-INH appears to be significantly higher than initially estimated (based on NBA utilisation data, the submission estimated that 36 patients would use C1-INH as routine prophylaxis in Year 1, while the MSAC estimated that 8 patients would be eligible for C1-INH in 2020). As such, the PBAC considered that conservative utilisation estimates would be required to reduce the risk of utilisation in a population that is likely to be cost-ineffective.

7.16 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 (per Paragraph 7.9).

7.17 The PBAC also considered that a [redacted]% rebate should apply for any usage above the total cap.

7.18 The PBAC considered the following issues would need to be addressed as part of the deferral, some of which would require stakeholder consultation:

- determine the appropriate baseline number and type of HAE attacks for lanadelumab eligibility to ensure use is targeted to a sufficiently high risk population and in whom there is more certainty that lanadelumab represents value-for-money;
- determine continuation criteria that ensure ongoing use is targeted to patients deriving appropriate clinical benefit;
- address the PBAC's concerns regarding the large difference in costs between the 300 mg Q4W and Q2W dosage regiments, despite the similarity in clinical outcomes between the regimens;
- address the PBAC's concerns regarding the economic model (as outlined above);
- update the financial estimates based on the population encompassed by any revisions to the restriction and to address the PBAC's concerns regarding the financial estimates; and
- provide an updated RSA proposal (as outlined above).

Outcome:
Deferred

8 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.

9 Sponsor's Comment

The sponsor had no comment.