

## 5.12 GARADACIMAB, Injection 200 mg in 1.2 mL pre-filled pen, TBD, CSL Behring (Australia) Pty Ltd.

### 1 Purpose of submission

- 1.1 The Category 1 submission requested a General Schedule Authority Required (Written) listing for the initial treatment and an Authority Required (Telephone/Online) listing for the continuing treatment of hereditary angioedema (HAE). Garadacimab was requested for listing for the routine prevention of HAE attacks in adult and adolescent patients (aged 12 years and older) with HAE Types I and II.
- 1.2 Listing was requested on the basis of a cost-minimisation approach (CMA) versus lanadelumab as long term prophylaxis (LTP) to prevent HAE attacks in the PBS target population.

**Table 1: Key components of the clinical issue addressed by the submission**

Component	Description
Population	Patients with hereditary angioedema Types I and II
Intervention	Garadacimab 200 mg in 1.2 mL subcutaneous injection
Comparator	Lanadelumab 300 mg in 2 mL subcutaneous injection
Outcomes	<p>Efficacy outcomes</p> <ul style="list-style-type: none"> <li>• Time-normalised number of attacks</li> <li>• Reduction in attack rate</li> <li>• Responder analysis (% of responders with specified % reductions in attacks)</li> <li>• Time-normalised number of attacks requiring on-demand treatment</li> <li>• Time-normalised number of moderate or severe attacks</li> <li>• Subject's Global Assessment of Response to Therapy</li> </ul> <p>Safety outcomes</p> <ul style="list-style-type: none"> <li>• Safety and tolerability profile (including adverse events)</li> </ul> <p>Exploratory outcomes</p> <ul style="list-style-type: none"> <li>• Angioedema Quality of Life</li> <li>• EQ-5D-5L</li> <li>• Work Productivity and Activity Impairment: General Health</li> <li>• Investigator's Global Assessment of Response to Therapy</li> <li>• Time to first attack</li> <li>• Attack severity</li> </ul>
Clinical claim	Non-inferior efficacy and safety to lanadelumab

Source: Table 1.1, p13 of the submission.  
EQ-5D-5L = EuroQoL-5 Dimension 5 Level

## 2 Background

### Registration status

- 2.1 TGA status at time of PBAC consideration: The Clinical Evaluation Reports (CERs, Round 1 and Round 2), and the Delegate’s Overview (DO) were available. The CERs and DO noted that the proposed indication was ‘for routine prevention of hereditary angioedema (HAE) attacks in adult and paediatric patients (aged 12 years and older)’ and raised uncertainties around use in adolescents and in patients with non C1-INH HAE. The PBAC noted the latter was not relevant to its consideration as the proposed PBS-listing would exclude non C1-INH HAE (i.e. listing was only requested for HAE Types I and II).
- 2.2 The Delegate’s Overview concluded “The efficacy of garadacimab for the claimed indication [with C1-INH HAE (C1-esterase inhibitor deficiency or dysfunction)] has been demonstrated, showing superiority over placebo. Treatment significantly reduced the rate of hereditary angioedema (HAE) attacks and increased the number of attack-free patients, indicating a clinically meaningful benefit. The safety profile appears generally favourable; however, there are important considerations regarding the target population and specific safety concerns, particularly related to its impact on the coagulation system.” The PBAC noted that any potential PBS listing of garadacimab cannot proceed until registration has been finalised.
- 2.3 Garadacimab was designated an orphan drug by the TGA for the routine prevention of recurrent HAE attacks. A filing to include garadacimab on the ARTG was accepted by the TGA on 2 January 2024 under the ACCESS Consortium Work-sharing Pathway. The TGA indication proposed by the sponsor was:
- ANDEMBRY® is indicated for routine prevention of recurrent hereditary angioedema (HAE) attacks in adult and paediatric patients (aged 12 years and older).
- 2.4 A new form of lanadelumab was also considered at the November 2024 PBAC meeting for the treatment of HAE Types 1 or 2 in patients aged 2 to 11 years (November 2024 PBAC agenda). Lanadelumab 150mg/1mL solution for injection was TGA-approved on 25 July 2024 for the routine prevention of recurrent attacks of hereditary angioedema (C1-esterase-inhibitor deficiency or dysfunction) in patients aged 2 years and older.

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

## 3 Requested listing

- 3.1 The restriction requested in the submission is outlined below.

### Requested listing - initiating

MEDICINAL PRODUCT medicinal product pack	Dispensed Price for Max. Qty	Max. qty packs	Max. qty units	No. of Rpts	Available brands
Garadacimab injection 200 mg in 1.2 mL pre-filled pen	Published: \$ Effective: TBD	2	2	0	ANDEMBRY

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<b>Category / Program:</b> General Schedule (Code GE)
<b>Prescriber type:</b> <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/>
<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required (in writing)– Postal/HPOS Upload
<b>Episodicity:</b> Chronic treatment
<b>Condition:</b> Hereditary angioedema Types I and II
<b>PBS indication:</b> Chronic treatment of hereditary angioedema Types I and II
<b>Treatment Phase:</b> Initial 1: New patient (commencing with no previous treatment with C1-INH or lanadelumab for routine prophylaxis)
<b>Clinical criteria:</b> Patient must have experienced at least 12 treated acute attacks of hereditary angioedema within the 6-month period prior to commencing treatment with this drug. AND Patient must not have been receiving a C1-esterase inhibitor through the National Blood Authority or lanadelumab through the Pharmaceutical Benefits Scheme as routine prophylaxis for hereditary angioedema at the time of application. AND The treatment must not be used in combination with a C1-esterase inhibitor concentrate or lanadelumab.
<b>Treatment criteria:</b> Must be treated by a clinical immunologist or a specialist allergist
<b>Population criteria:</b> Patient must be aged 12 years or older
<b>Prescribing Instructions:</b> For the purposes of administering this restriction, acute attacks of hereditary angioedema are those of a severity necessitating immediate medical intervention with either (i) icatibant, or (ii) C1-esterase inhibitor concentrate.  The baseline measurement of the number of treated acute attacks of hereditary angioedema within the 6 months prior to initiating treatment must be provided at the time of submitting this application.

<b>Category / Program:</b> General Schedule (Code GE)
<b>Prescriber type:</b> <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/>
<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required (in writing)– Postal/HPOS Upload
<b>Episodicity:</b> Chronic treatment
<b>Condition:</b> Hereditary angioedema Types I and II
<b>PBS indication:</b> Chronic treatment of hereditary angioedema Types I and II
<b>Treatment Phase:</b> Initial 2: New patient (commencing with National Blood Authority-funded C1-INH)
<b>Clinical criteria:</b> Patient must have been receiving a C1-esterase inhibitor through the National Blood Authority as routine prophylaxis for hereditary angioedema immediately prior to receiving garadacimab. AND The treatment must not be used in combination with a C1-esterase inhibitor concentrate or lanadelumab.
<b>Treatment criteria:</b> Must be treated by a clinical immunologist or a specialist allergist
<b>Population criteria:</b> Patient must be aged 12 years or older

<b>Category / Program:</b> General Schedule (Code GE)
<b>Prescriber type:</b> <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/>
<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required (in writing)– Postal/HPOS Upload
<b>Episodicity:</b> Chronic treatment
<b>Condition:</b> Hereditary angioedema Types I and II
<b>PBS indication:</b> Chronic treatment of hereditary angioedema Types I and II
<b>Treatment Phase:</b> Initial 3: New patient (commencing with PBS-funded lanadelumab)

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<p><b>Clinical criteria:</b>                  Patient must have been receiving lanadelumab through PBS as routine prophylaxis for hereditary angioedema immediately prior to receiving garadacimab,                  AND                  The treatment must not be used in combination with a C1-esterase inhibitor concentrate or lanadelumab.</p>
<p><b>Treatment criteria:</b> Must be treated by a clinical immunologist or a specialist allergist</p>
<p><b>Population criteria:</b> Patient must be aged 12 years or older</p>

**Requested restriction – continuing**

MEDICINAL PRODUCT medicinal product pack	Dispensed Price for Max. Qty	Max. qty packs	Max. qty units	No. of Rpts	Available brands
Garadacimab injection 200 mg in 1.2 mL pre-filled pen	Published: \$ Effective: TBD	1	1	5	ANDEMBRY

<p><b>Category / Program:</b> General Schedule (Code GE)</p>
<p><b>Prescriber type:</b> <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/></p>
<p><b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required (telephone or OPA immediate assessment)</p>
<p><b>Episodicity:</b> Chronic treatment</p>
<p><b>Condition:</b> Hereditary angioedema Types I and II</p>
<p><b>PBS indication:</b> Chronic treatment of hereditary angioedema Types I and II</p>
<p><b>Treatment Phase:</b> Continuing preventative treatment</p>
<p><b>Clinical criteria:</b>                  Patient must have previously received PBS-subsidised treatment with this drug for this condition.                  AND                  Patient must have demonstrated or sustained an adequate response to PBS-subsidised treatment with this drug for this condition.                  AND                  The treatment must not be PBS-subsidised in combination with a C1-esterase inhibitor concentrate or lanadelumab.</p>
<p><b>Treatment criteria:</b> Must be treated by a clinical immunologist or a specialist allergist, or in consultation with a specialist allergist or clinical immunologist</p>
<p><b>Population criteria:</b> Patient must be aged 12 years or older</p>
<p><b>Prescribing Instructions:</b>                  For the purposes of administering this restriction, an adequate response is a reduction of the baseline number of acute attacks of hereditary angioedema of a severity necessitating immediate medical intervention with either (i) icatibant, or (ii) C1-esterase inhibitor concentrate. The details of the reduction must be documented in the patient's medical records for auditing purposes.</p>

**Requested restriction – grandfathering**

MEDICINAL PRODUCT medicinal product pack	Dispensed Price for Max. Qty	Max. qty packs	Max. qty units	No. of Rpts	Available brands
Garadacimab injection 200 mg in 1.2 mL pre-filled pen	Published: \$ Effective: TBD	1	1	0	ANDEMBRY

<p><b>Category / Program:</b> General Schedule (Code GE)</p>
<p><b>Prescriber type:</b> <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/></p>
<p><b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required (in writing)-Postal/HPOS Upload</p>
<p><b>Episodicity:</b> Chronic treatment</p>
<p><b>Condition:</b> Hereditary angioedema Types I and II</p>
<p><b>PBS indication:</b> Chronic treatment of hereditary angioedema Types I and II</p>

<b>Treatment Phase:</b> new patient (commencing from non-PBS-funded garadacimab)
<b>Clinical criteria:</b> Patient must have previously received non-PBS subsidised treatment with this drug for this condition as routine prophylaxis for hereditary angioedema prior to [listing date]. AND The treatment must not be PBS-subsidised in combination with a C1-esterase inhibitor concentrate or lanadelumab.
<b>Treatment criteria:</b> Must be treated by a clinical immunologist or a specialist allergist, or in consultation with a specialist allergist or clinical immunologist
<b>Population criteria:</b> Patient must be aged 12 years or older
<b>Prescribing Instructions:</b> For the purposes of administering this restriction, an adequate response is a reduction of the baseline number of acute attacks of hereditary angioedema of a severity necessitating immediate medical intervention with either (i) icatibant, or (ii) C1-esterase inhibitor concentrate. The details of the reduction must be documented in the patient's medical records for auditing purposes.

- 3.2 The proposed published ex-manufacturer price was \$ [REDACTED] per pack of garadacimab. The submission proposed a Special Pricing Arrangement (SPA) with the effective price of garadacimab to be determined on a cost-minimisation basis versus lanadelumab at its confidential effective price.
- 3.3 The submission proposed the PBS listing of garadacimab for patients with HAE Types I and II. The requested initiation restrictions included the following patient groups: (1) new patients who have experienced at least 12 treated acute attacks of HAE within a period of 6 months with no previous treatment with C1-INH or lanadelumab for routine prophylaxis; (2) new patients commencing from National Blood Authority (NBA)-funded C1-INH; and (3) patients commencing from PBS-funded lanadelumab. The requested grandfathering restriction would also enable a small number of patients accessing garadacimab under a special access scheme to continue the therapy under a PBS listing. Patients with HAE Types I and II who are receiving PBS-subsidised garadacimab treatment and who demonstrate adequate response to the treatment will be eligible to continue the treatment.
- 3.4 The proposed PBS restrictions for garadacimab are aligned with the current lanadelumab PBS listings for the chronic treatment of HAE Types I and II. The requirement for the patient to have experienced 12 acute attacks of HAE within the 6-month period (equivalent to 2 attacks per month) prior to commencing garadacimab appears stricter than the eligibility criteria of the key trial VANGUARD ( $\geq 3$  HAE attacks during the 3 months before screening, equivalent to 1 attack per month). However, as the mean number of attacks during the 3 months before screening or start of HAE prophylaxis was 3.0 attacks per month in VANGUARD, with a 95% confidence interval (CI) of 2.3-3.7 attacks, the number of attacks at baseline in the trial population may reflect the proposed target population.
- 3.5 The initial restriction for lanadelumab provides up to six months of treatment, whereas the submission's proposed initial restriction for garadacimab would only provide the first month of treatment (i.e. the proposed initial restriction of two units with no repeats would cover the loading dose only). The evaluation considered that it was unclear whether one month would be sufficient to demonstrate an adequate

response to treatment, i.e. a reduction in the baseline number of acute attacks of HAE of a severity necessitating immediate medical intervention with either icatibant or C1-INH. The pre-PBAC response stated that the sponsor would be willing to accept an initiating restriction that allows for up to six months of treatment.

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

## 4 Population and disease

- 4.1 HAE is a rare genetic disorder that is potentially severely debilitating and life-threatening. It is manifested as transient and asymmetric attacks of cutaneous and submucosal swelling of the face, upper airways, extremities, gastrointestinal tract, and/or genitalia. The recurring attacks with unpredictable frequency, intensity, and duration place a burden on the daily life of patients. Surgical or dental procedures can also trigger HAE attacks. The number of individuals effected by HAE is estimated to be around 480, with a prevalence of approximately 1 in 54,000 in Australia<sup>1</sup>.
- 4.2 HAE is inherited as an autosomal dominant trait. HAE Types I and II are caused by mutations in the C1-INH gene, resulting in the deficiency of C1-INH (HAE Type I) or the dysfunction of C1-INH (HAE Type II).
- 4.3 Attack frequency and severity among patients is variable. Most patients who experience fewer attacks can be managed by on-demand treatment such as icatibant administered subcutaneously (SC) or C1-INH concentrate (Berinert®) intravenous (IV) injection. Berinert IV is also used as short term prophylaxis for patients undergoing surgical or dental procedures. Patients who experience multiple attacks per month can receive LTP such as Berinert SC (for patients aged ≥ 8 years who experience HAE attacks ≥ 8 per month), funded through the NBA's National Product List (NPL)<sup>2</sup>, or PBS subsidised lanadelumab (for patients aged ≥ 12 years who experience HAE attacks ≥ 12 in a 6-month period).
- 4.4 Garadacimab is a fully human recombinant monoclonal antibody that specifically inhibits activated Factor XII to prevent the generation of excessive bradykinin, which is responsible for HAE attacks. Lanadelumab is also involved in the bradykinin pathway but is a kallikrein inhibitor.
- 4.5 Garadacimab is intended to be used as the routine prevention of HAE attacks in patients aged ≥ 12 years who experience HAE attacks ≥ 12 per 6 months. The recommended dose is an initial loading dose of 400 mg administered SC as two 200 mg injections on the first day of treatment, followed by 200 mg SC once per month.

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

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<sup>1</sup> Maurer M *et al.* The international WAO/EAACI guideline for the management of hereditary angioedema - The 2021 revision and update. *World Allergy Organ J.* 2022; 15(3): 100627

<sup>2</sup> National Blood Agreement. URL: <https://www.blood.gov.au/national-blood-agreement>

## 5 Comparator

- 5.1 Lanadelumab was nominated as the main comparator in the submission. The main arguments in support of the nomination were: 1) lanadelumab is the most commonly used medication as LTP for patients with HAE Types I and II in Australia; and 2) it has a similar clinical place as garadacimab in the HAE management pathway.
- 5.2 The evaluation and the ESC considered that lanadelumab was the appropriate comparator.

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

## 6 Consideration of the evidence

### Sponsor hearing

- 6.1 There was no hearing for this item.

### Consumer comments

- 6.2 The PBAC noted and welcomed the input from individuals (20), health care professionals (5) and an organisation (1) via the Consumer Comments facility on the PBS website.
- 6.3 The comments (including comments from individuals living with HAE and their caregivers, and from HAE Australia) described the debilitating physical and quality of life impacts of HAE attacks, due to both the attacks themselves and also due to the fear of attacks which can be unpredictable and life-threatening. HAE Australia explained that HAE attacks can be painful, and the condition can cause significant physical and emotional distress, and can impact on a patient's ability to work, maintain relationships and engage in everyday activities.
- 6.4 The comments described the challenges of treating attacks with ODT (e.g. icatibant and C1-INH) and the varying levels of response to other prophylactic therapies (e.g. lanadelumab, C1-INH and danazol), with many patients reporting adequate control of attacks, while others reported continued frequent hospitalisations. HAE Australia and consumers who have accessed garadacimab described the value of: self-administration (given garadacimab is administered by sub-cutaneous injection); less frequent dosing; less stringent refrigeration requirements (e.g. garadacimab can be may be stored at room temperature for up to 2 months, which may be more convenient for travel); and fewer adverse effects (e.g. injection site reactions).
- 6.5 Health professionals outlined the clinical trial results and noted that some patients treated with garadacimab have experienced complete control of HAE attacks. Health professionals noted the wide range of attack frequency, and outlined that only some patients are on any form of preventive treatment.

## Clinical trials

- 6.6 No head-to-head trials were identified for a direct comparison between garadacimab and lanadelumab as LTP in the proposed PBS target population. The submission was based on one randomised controlled trial which compared garadacimab to placebo (VANGUARD), and one comparing lanadelumab to placebo (HELP), to inform an anchored indirect treatment comparison (ITC) of garadacimab versus lanadelumab, using the Bucher method<sup>3</sup> via placebo as the common reference.
- 6.7 The HELP trial has previously been reviewed by the PBAC when the lanadelumab submissions were considered.
- 6.8 Details of the key trials presented in the submission are provided in Table 2.

**Table 2: Trials and associated reports presented in the submission**

Trial ID	Protocol title/ Publication title	Publication citation
VANGUARD CSL312-3001 NCT04656418	A multicenter, double-blind, randomized, placebo-controlled, parallel-arm study to Investigate the efficacy and safety of subcutaneous administration of CSL312 (garadacimab) in the prophylactic treatment of hereditary angioedema. Clinical Study Report. Craig TJ, Reshef A, et al. Efficacy and safety of garadacimab, a factor XIIa inhibitor for hereditary angioedema prevention (VANGUARD): a global, multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. Craig T., Magerl M., et al. Efficacy and safety of subcutaneous garadacimab for the prophylaxis of hereditary angioedema attacks in adults and adolescent patients with HAE: results from a multicenter, placebo-controlled Phase 3 trial.	06 October 2022  Lancet 2023; 401(10382):1079-1090  Journal of Allergy and Clinical Immunology 2023; 151:2 Suppl (AB132)
VANGUARD CSL312-3001 NCT04739059	Anderson J., Levy D, et al. Long-term safety and efficacy with garadacimab for hereditary angioedema prophylaxis in an open-label extension study.	Annals of Allergy, Asthma & Immunology 2023; 131: S3-S13
VANGUARD	Jacobs J., Magerl M., et al. Garadacimab for hereditary angioedema prophylaxis in adolescents: efficacy and safety from the Phase 3 (VANGUARD) study and open-label extension (second interim analysis).	Journal of Allergy and Clinical Immunology 2024; 153:2 Suppl (AB6)
HELP NCT02741596	Banerji A, Riedl MA, et al. Effect of lanadelumab compared with placebo on prevention of hereditary angioedema attacks: a randomized clinical trial. Riedl MA, Maurer M, et al. Lanadelumab demonstrates rapid and sustained prevention of hereditary angioedema attacks <sup>a</sup> Banerji A, Bernstein JA, et al. Long-term prevention of hereditary angioedema attacks with lanadelumab: the HELP OLE study <sup>a</sup>	JAMA 2018; 320(20): 2108-2121  Allergy. 2020;75(11):2879-2887  Allergy. 2022;77(3):979-990

Source: Table 2.3 & 2.4, pp42, 44 of the submission

<sup>a</sup> Data from the Riedl et al (2020) and Banerji et al (2022) publication was not used in the indirect comparison.

Blue shading indicates the trial/publication previously considered by the PBAC (for lanadelumab).

- 6.9 The key features of the included evidence for the ITC are summarised in Table 3. The ITC was conducted via placebo as the common reference.

<sup>3</sup> Bucher HC *et al.* The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. *J Clin Epidemiol.* 1997;50(6):683-91.

**Table 3: Key features of the included evidence (indirect comparison)**

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
<b>Garadacimab vs. placebo</b>						
VANGUARD	64	R, DB 6 mths	Low <sup>a</sup>	HAE Types I and II patients aged ≥ 12 years with ≥ 1 HAE attack per 4 weeks	<ul style="list-style-type: none"> <li>• Time-normalised number of HAE attacks</li> <li>• Time-normalised number of HAE attacks requiring on-demand treatment</li> <li>• Time-normalised number of moderate and/or severe HAE attacks</li> <li>• Proportion of attack-free patients over treatment period</li> <li>• Change from baseline in Angioedema-QoL total score</li> <li>• Any TEAEs</li> <li>• Serious AEs</li> </ul>	No
<b>Lanadelumab vs. placebo</b>						
HELP	125 <sup>b</sup>	R, DB 26 wks	Low <sup>a</sup>	HAE Types I and II patients aged ≥ 12 years with ≥ 1 HAE attacks per 4 weeks	As above	No

Source: Compiled during the evaluation based on information provided in Section 2.2-2.3 of the submission.

AE = adverse event; DB = double blind; HAE = hereditary angioedema; mths = months; QM = once per month; R = randomised; TEAE = treatment-emergent adverse event; wks = weeks

<sup>a</sup> Although the risk of bias was considered low in each individual trial, the risk of bias of the indirect comparison was considered high due to the transitivity issues between the trials.

<sup>b</sup> A total of four treatments arms were included in the HELP trial: lanadelumab 300 mg every 2 weeks (Q2W) (N=27), lanadelumab 300 mg every 4 weeks (Q4W) (N=29), lanadelumab 150 mg Q4W (N=28) and placebo (N=41). Efficacy and safety data from the lanadelumab 300 mg Q2W and 300 mg Q4W treatment arms (the two dosing regimens recommended in the lanadelumab product information) and the placebo arm were used in the indirect treatment comparison.

Blue shading indicates the clinical trial previously considered by PBAC (for lanadelumab)

6.10 VANGUARD was a Phase 3, randomised, double-blind, placebo-controlled trial comparing garadacimab (400 mg SC as the loading dose followed by 200 mg SC once per month) versus placebo as the routine prophylaxis for acute HAE attacks in patients aged 12 years and older with HAE Types I and II during a 6-month treatment period. After a screening period (up to 1 month), patients underwent a run-in period (up to 2 months) to determine their baseline attack rate. Participants who met a minimum baseline rate of at least 1 investigator-confirmed HAE attack per month were eligible for enrolment. A total of 65 participants completed the run-in period and were randomised to garadacimab or placebo at a 3:2 ratio. One patient in the placebo arm who was randomised to blinded treatment in error and never received the study treatment was not included in the analysis. The evaluation considered that the risk of bias in the VANGUARD trial was low, and the baseline characteristics, including the baseline HAE attack rate, were generally balanced between the two treatment arms in VANGUARD.

6.11 In VANGUARD, only one among the 65 randomised patients (1.6%) had used lanadelumab as routine prophylaxis of HAE attacks before enrolment; whereas in Australian clinical practice, lanadelumab is the most commonly used routine

prophylactic treatment for HAE. The evaluation and the ESC noted that evidence regarding the efficacy and safety of the use of garadacimab following lanadelumab was lacking. The ESC acknowledged that this remains an area of uncertainty, as is the use of lanadelumab following garadacimab. However, the ESC considered that it would be reasonable to allow sequential use given the slightly different mechanisms of action and dosing frequency.

- 6.12 HELP was a Phase 3, multicentre, randomised, double-blind, placebo-controlled trial comparing three dose regimens of lanadelumab with placebo as routine prophylaxis for acute attacks in patients aged 12 years and older with HAE Types I and II during a 26-week treatment period. A total of 125 patients were randomised to receive lanadelumab or placebo with a ratio of 2:1. Patients assigned to lanadelumab were further randomised 1:1:1 to one of the three dose regimens: (1) lanadelumab 300 mg SC Q2W, (2) lanadelumab 300 mg SC every 4 weeks (Q4W), and (3) lanadelumab 150 mg SC Q4W. Efficacy and safety data from the lanadelumab 300 mg Q2W treatment arm (N = 27), the lanadelumab 300 mg Q4W treatment arm (N = 29) (the two dosing regimens recommended in the lanadelumab product information [PI]) and the placebo arm (N = 41) of the HELP trial were used in the ITC.
- 6.13 The evaluation identified a number of key differences across the VANGUARD and HELP trials:
- A higher baseline mean and median numbers of HAE attacks per month in the HELP population compared to the VANGUARD population (mean: 3.7 vs. 3.0; median 3.0 vs. 2.0).
  - A higher percentage of patients in HELP had received LTP to prevent HAE attacks within the 3 months prior to screening compared to VANGUARD (56.0% vs. 32.8%). The evaluation considered that this, in combination with the more frequent HAE attacks at baseline in the HELP trial, suggested that the trial participants in HELP had more severe disease compared to the VANGUARD population.
  - VANGUARD was conducted 4 years later than HELP and, therefore, it is possible that more LTP options were available to the VANGUARD patient population compared to the HELP patient population.
  - The percentage of female patients in VANGUARD was slightly lower than that in HELP (59.4% vs. 70.4%).
- 6.14 Compared with VANGUARD, HELP had additional criteria to define an investigator-confirmed HAE attack which included: 1) if an HAE attack was 8 hours or less on a particular day that day was considered attack-free (HELP trial Statistical Analysis Plan, p28); and 2) if the patient-reported event was accompanied by symptoms that were not consistent with an attack, such as urticaria, the investigator may still determine clinically that the event did not represent an HAE attack (HELP Clinical Trial Protocol, p134). The evaluation considered that given the differential criteria in defining an HAE

attack, it was possible that some HAE attacks reported in VANGUARD would not be defined as HAE attacks if they occurred in HELP, potentially leading to an underreporting of the number of HAE attacks in HELP compared to VANGUARD). The Pre-Sub-Committee Response (PSCR) maintained that the HELP and VANGUARD trial definitions were likely to be similar “as the majority of observed attacks in the HELP trial were longer than 12 hours in duration”. The ESC considered that the differences in the definitions of HAE attacks between the two trials were unlikely to have a substantial impact as most HAE attacks usually last  $\geq 8$  hours.

- 6.15 In the submission, an ITC regarding the efficacy and safety of garadacimab versus lanadelumab was conducted between: 1) garadacimab 200 mg SC once per month (QM) and lanadelumab 300 mg Q2W, and 2) garadacimab 200 mg SC QM and lanadelumab 300 mg Q4W. Of note, when the PBAC considered the lanadelumab resubmission at the July 2021 meeting, the PBAC recalled that, based on the clinical evidence from HELP, the lanadelumab Q4W regimen did not demonstrate a significant difference in efficacy compared to the Q2W regimen, and that there was residual uncertainty in the magnitude of the benefit due to the small patient numbers in the HELP trial and potential applicability issues (para 7.4, lanadelumab public summary document [PSD], July 2021 PBAC meeting).

### **Comparative effectiveness**

- 6.16 A summary of the efficacy results in the garadacimab arm versus placebo arm in VANGUARD is provided in Table 4.

**Table 4: Summary of efficacy outcomes in VANGUARD (ITT population)**

Endpoint		Garadacimab 200 mg QM (N = 39)	Placebo (N=25)
Number of evaluable subjects, n (%) <sup>a</sup>		39 (100.0)	24 (96.0)
<b>Primary endpoint</b>			
Time-normalised number of HAE attacks per month during the treatment period	Number of HAE attacks during treatment period, n	63	264
	Time-normalised number of HAE attacks per month		
	Mean (95% CI) [SD]	<b>0.27 (0.05, 0.49) [0.68]</b>	<b>2.01 (1.44, 2.57) [1.34]</b>
	Median (inter-quartile range)	0.00 (0.00, 0.31)	1.35 (1.00, 3.20)
	Min, Max	0.00, 3.8	0.2, 4.4
Two-sided Wilcoxon test, p-value		<b>&lt;0.001</b>	
<b>Secondary efficacy endpoints</b>			
Reduction in the HAE attack rate during the treatment period compared to the run-in period	Reduction in time-normalised number of HAE attacks per month <sup>b</sup>		
	Mean (SD)	90.67 (22.43)	20.21 (42.66)
	95% CI	(83.40, 97.94)	(2.20, 38.22)
Two-sided Wilcoxon test, nominal p-value		<b>&lt; 0.001</b>	
Time-normalised number of HAE attacks per month requiring on-demand treatment during the treatment period	Number of HAE attacks during treatment period, n	63	264
	Number of HAE attacks requiring on-demand treatment during treatment period, n (%) <sup>c</sup>	54 (85.7)	245 (92.8)
	Time-normalised number of HAE attacks requiring on-demand treatment per month		
	Mean (SD)	0.23 (0.66)	1.86 (1.41)
	95% CI	(0.02, 0.45)	(1.26, 2.46)
Two-sided Wilcoxon test, nominal p-value		<b>&lt; 0.001</b>	
Time-normalised number of moderate or severe HAE attacks per month during the treatment period	Number of HAE attacks during treatment period, n	63	264
	Number of moderate or severe HAE attacks during treatment period, n (%) <sup>c</sup>	29 (46.0)	172 (65.2)
	Time-normalised number of moderate or severe HAE attacks per month		
	Mean (SD)	0.13 (0.30)	1.35 (1.17)
	95% CI	(0.03, 0.22)	(0.86, 1.84)
Two-sided Wilcoxon test, nominal p-value		<b>&lt; 0.001</b>	
Percentage reduction in monthly HAE attack rate during the treatment period	Responders with a ≥ 50% reduction of attack rate, n	37	8
	Percentage of responders (95% CI) <sup>d</sup>	94.9 (83.1, 98.6)	33.3 (18.0, 53.3)
	Responders with a ≥ 70% reduction of attack rate, n	36	4
	Percentage of responders (95% CI) <sup>d</sup>	92.3 (79.7, 97.4)	16.7 (6.7, 35.9)
	Responders with a ≥ 90% reduction of attack rate, n	29	2
	Percentage of responders (95% CI) <sup>d</sup>	74.4 (58.9, 85.4)	8.3 (2.3, 25.9)
	Responders with a 100% reduction (attack-free), n	24	0
Percentage of attack-free patients (95% CI) <sup>d</sup>	61.5 (45.9, 75.1)	0.0 (0.0, 13.8)	
Fisher exact test, nominal p-value		<b>&lt; 0.001</b>	

Source: Compiled during the evaluation, based on Tables 2.20 to 2.24, pp85-92 of the submission. **Results in bold are statistically significant**

CI = confidence interval; HAE = hereditary angioedema; ITT = intention-to-treat; Max = maximum; Min = minimum; QM = once per month; SD = standard deviation

<sup>a</sup> Percentages were based on the ITT analysis set. The number of evaluable subjects included those with a treatment period of at least 30 day.

<sup>b</sup> The percentage reduction in the time-normalised number of HAE attacks was calculated within a subject as:  $100 * [1 - (\text{time-normalised number of HAE attacks per month during treatment period} / \text{time-normalised number of HAE attacks per month during run-in period})]$ .

<sup>c</sup> Percentages were based on number of HAE attacks during treatment period for respective treatment group

<sup>d</sup> The 95% CI was based on Wilson's asymptotic confidence limits.

- 6.17 Patients treated with garadacimab 200 mg SC QM for 6 months (182 days) had a lower time-normalised number of HAE attacks per month, compared to patients treated with placebo for the same length of time (mean 0.27 [SD<sup>4</sup> 0.68] vs. 2.01 [SD 1.34]). Garadacimab was associated with a statistically significant reduction in the time-normalised number of HAE attacks per month ( $p < 0.001$ , two-sided Wilcoxon test) compared with placebo.
- 6.18 The mean reduction in the time-normalised number of HAE attacks during the 6-month treatment period compared to the run-in period was 90.7% (SD: 22.4%) in the garadacimab arm and 20.2% (SD: 42.7%) in the placebo arm (nominal  $p < 0.001$ ). Responder analysis showed that, during the entire 6-month treatment period, the proportions of patients who had a  $\geq 50\%$  reduction in the monthly attack rate and who were attack-free (i.e., 100% reduction in HAE attacks) were consistently higher in the garadacimab arm than in the placebo arm ( $\geq 50\%$  reduction: 94.9% vs. 33.3%; attack-free: 61.5% vs. 0%); and the difference was statistically significant.
- 6.19 In the garadacimab arm, a total of 63 HAE attacks were experienced by 15 patients (38.5%) during the 6-month treatment period and 85.7% of these attacks (54 attacks) required on-demand treatment. In the placebo arm, a total 264 HAE attacks were experienced by all 24 patients and 92.8% of these attacks (245 attacks) required on-demand treatment. The mean time-normalised number of HAE attacks per month requiring on-demand treatment was significantly lower for garadacimab versus placebo (0.23 [SD: 0.66] vs. 1.86 [SD: 1.41]). Similar results were also reported for the time-normalised number of moderate or severe HAE attacks (0.13 [SD: 0.30] in garadacimab vs. 1.35 [SD: 1.17] in placebo).
- 6.20 At the end of the treatment period (Day 182), 65.8% and 15.8% of patients in the garadacimab arm rated the treatment as “excellent” and “good” by the Subject’s Global Assessment of Response to Therapy (SGART), respectively, compared to 12.5% and 20.8%, respectively, in the placebo group.
- 6.21 In general, patients receiving garadacimab had improved quality of life compared to patients receiving placebo. In the garadacimab arm, the reduction in the mean (SD) total score in the Angioedema Quality of Life (Angioedema QoL) questionnaire (indicating better health status) was -23.7 (15.8) from baseline to Day 31 and -26.5 (17.9) from baseline to Day 182; both reductions were clinically meaningful<sup>5</sup>. On the

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<sup>4</sup> Standard deviation

<sup>5</sup> A reduction of  $\geq 6$  points in Angioedema QoL score was considered clinically relevant. A lower score means better quality of life.

other hand, in the placebo arm, the reduction in the mean total score from baseline was less than 6 points at any timepoint during the entire treatment period. For the EuroQoL-5 Dimension-5 Level (EQ-5D-5L), there was some improvement in the mean health state utility value (HSV) and Visual Analogue Scale (VAS) scores in the garadacimab group compared to placebo.

### Indirect comparison of garadacimab versus lanadelumab

6.22 The results of the ITCs for the efficacy endpoints for garadacimab relative to lanadelumab are presented in Table 5 and Table 6.

**Table 5: Indirect comparison of time-normalised numbers of HAE attacks, attacks requiring on-demand treatment, and moderate and/or severe attacks during the treatment period in VANGUARD and HELP**

	VANGUARD		HELP			
	GARA 200 mg QM (N=39)	PBO (N=24)	LANA 300 mg Q2W (N=27)	PBO (N=41)	LANA 300 mg Q4W (N=29)	PBO (N=41)
<b>Time-normalised number of HAE attacks per month during the treatment period</b>						
Mean (95% CI)	0.3 (0.05, 0.49)	2.01 (1.44, 2.57)	0.26 (0.14, 0.46)	1.97 (1.64, 2.36)	0.53 (0.36, 0.77)	1.97 (1.64, 2.36)
Difference (95% CI)	-1.7 (-2.3, -1.2)		-1.7 (-2.1, -1.3)		-1.4 (-1.8, -1.0)	
ITC: GARA vs. LANA	GARA vs. LANA 300mg Q2W: 0.0 (-0.7, 0.7)				GARA vs. LANA 300mg Q4W: -0.3 (-1.0, 0.4)	
p-value	0.94				0.41	
<b>Time-normalised number of HAE attacks per month requiring on-demand treatment during the treatment period</b>						
Mean (95% CI)	0.23 (0.02, 0.45)	1.86 (1.26, 2.46)	0.21 (0.11, 0.40)	1.64 (1.34, 2.01)	0.42 (0.28, 0.65)	1.64 (1.34, 2.01)
Difference (95% CI)	-1.6 (-2.2, -1.0)		-1.4 (-1.8, -1.1)		-1.2 (-1.6, -0.9)	
ITC: GARA vs. LANA	GARA vs. LANA 300mg Q2W: -0.2 (-0.9, 0.5)				GARA vs. LANA 300mg Q4W: -0.4 (-1.1, 0.3)	
p-value	0.58				0.24	
<b>Time-normalised number of moderate/severe HAE attacks per month during the treatment period</b>						
Mean (95% CI)	0.13 (0.03, 0.22)	1.35 (0.86, 1.84)	0.20 (0.11, 0.39)	1.22 (0.97, 1.52)	0.32 (0.20, 0.53)	1.22 (0.97, 1.52)
Difference (95% CI)	-1.2 (-1.7, -0.8)		-1.0 (-1.3, -0.7)		-0.9 (-1.2, -0.6)	
ITC: GARA vs. LANA	GARA vs. LANA 300mg Q2W: -0.2 (-0.8, 0.3)				GARA vs. LANA 300mg Q4W: -0.3 (-0.9, 0.2)	
p-value	0.47				0.25	

Source: Table compiled during the evaluation, based on Tables 2.51, 2.52 and 2.55, pp127-128, 131 of the submission.  
 CI = confidence interval; GARA = garadacimab; HAE = hereditary angioedema; LANA = lanadelumab; N = number of patients in the treatment arm; PBO = placebo; QM = once per month; Q2W = once every 2 weeks; Q4W = once every 4 weeks  
 Note: an ITC result of < 0 indicates a result favouring garadacimab

**Table 6: Indirect comparison of attack-free patients during the treatment period in VANGUARD and HELP**

Trial ID	Comparison	Intervention n/N (%)	Placebo n/N (%)	OR (95% CI)	RR (95% CI)	RD (95% CI)
<b>GARA 200 QM vs LANA 300 Q2W</b>						
VANGUARD	GARA 200 QM vs Placebo	24/39 (61.5%)	0/25 (0.0%)	80.61 (4.57, 1422.09)	31.85 (2.02, 501.25)	61.5% (46.3%, 76.8%)
HELP	LANA 300 Q2W vs Placebo	12/27 (44.4%)	1/41 (2.4%)	32.00 (3.82, 267.82)	18.22 (2.51, 132.16)	42.0% (22.7%, 61.3%)
Indirect comparison	GARA 200 QM vs LANA 300 Q2W			2.52 (0.07, 89.58)	1.75 (0.06, 52.14)	19.5% (-5.1%, 44.2%)
p-value	-			>0.05		
<b>GARA 200 QM vs LANA 300 Q4W</b>						
VANGUARD	GARA 200 QM vs Placebo	24/39 (61.5%)	0/25 (0.0%)	80.61 (4.57, 1422.09)	31.85 (2.02, 501.25)	61.5% (46.3%, 76.8%)
HELP	LANA 300 Q4W vs Placebo	9/29 (31.0%)	1/41 (2.4%)	18.00 (2.13, 152.17)	12.72 (1.70, 95.02)	28.6% (11.1%, 46.1%)
Indirect comparison	GARA 200 QM vs LANA 300 Q4W			4.48 (0.13, 160.15)	2.50 (0.08, 76.0)	32.9% (9.7%, 56.2%)
p-value	-			>0.05		0.00545

Source: Table 2.53, p129 of the submission

CI = confidence interval; GARA = garadacimab; LANA = lanadelumab; N = number of patients in the treatment arm; n = number of attack-free patients; OR = odds ratio; QM = once per month; Q2W = once every 2 weeks; Q4W = once every 4 weeks; RD = risk difference; RR = relative risk

Note: An indirect RD of > 0 or an indirect RR/OR of > 1 indicates a result favouring garadacimab

6.23 The ITC results of the time-normalised numbers of HAE attacks, HAE attacks requiring on-demand treatment, and moderate/severe HAE attacks numerically favoured garadacimab 200 mg QM compared with lanadelumab 300 mg Q2W, and the 95% CIs did not include a worsening of outcomes which was clinically relevant. The point estimates of the indirect risk differences (RDs), relative risks (RRs) and odds ratios (ORs) for attack-free patients also numerically favoured garadacimab 200 mg QM versus lanadelumab 300 mg Q2W. However, the evaluation considered that the wide 95% CIs suggested that the ITC was not sufficiently powered to reliably assess the relative treatment effect for this outcome. Similar results were reported for the ITCs of garadacimab 200 mg QM versus lanadelumab 300 mg Q4W. The ESC noted the uncertainty arising from the small number of patients in the HAE trials, but considered the results were generally supportive of non-inferior efficacy.

6.24 The evaluation considered that key uncertainties relating to the ITCs for the efficacy between garadacimab 200 mg QM and lanadelumab 300 mg Q2M or Q4W included:

- the transitivity concerns and small number of patients in individual trials;
- not all endpoints reported in VANGUARD were included in the ITC, and the rationale of the selection of the endpoints (for example, selecting the outcome of responders with reduction in HAE attacks of 100%, i.e. attack-free, instead of other responder thresholds) was not provided in the submission.

6.25 The PSCR provided the results of subgroup analyses from the VANGUARD trial in order to address the concerns raised in the evaluation regarding differences in baseline characteristics between the VANGUARD and HELP trials. The subgroup analyses

included the number of HAE attacks at baseline and prior LTP use. The PSCR stated that these analyses showed that the primary outcome ‘was stable across all subgroups, with no significant treatment interaction effect detected for any subgroup.’ The ESC considered that the subgroup analyses provided with the PSCR were generally supportive of transitivity between the trials.

- 6.26 Overall, the ESC noted the similar rates of on-trial HAE attacks in the placebo groups in both trials, including similar rates of moderate and severe attacks, and thus considered it was likely that patients in the VANGUARD trial had similar disease severity compared to those in the HELP trial.
- 6.27 The PSCR also presented the results of a matching adjusted indirect comparison (MAIC) between garadacimab and lanadelumab. The PSCR stated that the results of the MAIC were generally favourable towards garadacimab for many of the outcomes, however the analysis could not be evaluated as the PSCR did not provide any information about the methodology.

## Comparative harms

- 6.28 Table 7 summarises the overall treatment-emergent adverse events (TEAEs) in the garadacimab treatment arm and the placebo arm in VANGUARD.

**Table 7: Summary of overall TEAEs in the VANGUARD study**

	Garadacimab 200 mg QM (N = 39) n (%)	Placebo (N = 25) n (%)
Any TEAE	25 (64.1)	15 (60.0)
Occurring within 24 hours after SC loading dose	2 (5.1)	2 (8.0)
Occurring Within 24 hours after any SC dose	6 (15.4)	6 (24.0)
Related to study treatment	4 (10.3)	3 (12.0)
Leading to study discontinuation	0	0
TEAEs by severity		
Mild	16 (41.0)	15 (60.0)
Related to study treatment	3 (7.7)	3 (12.0)
Moderate	16 (41.0)	7 (28.0)
Related to study treatment	1 (2.6)	0
Severe	1 (2.6)	0
Related to study treatment	0	0
TEAEs by outcome		
Death	0	0
Not recovered or not resolved	3 (7.7)	3 (12.0)
Recovered or resolved	24 (61.5)	14 (56.0)
Recovered or resolved with sequelae	2 (5.1)	0
Recovering or resolving	3 (7.7)	2 (8.0)
TEAEs identified as ISR	2 (5.1)	3 (12.0)
Related to study treatment	2 (5.1)	2 (8.0)
Treatment-emergent AESI as identified by the investigator	0	0
Serious TEAEs	1 (2.6)	0

Source: Table 2.40, p113 of the submission

AESI = adverse events of special interest; ISR = injection site reaction; N = number of subjects in the safety analysis set; n = number of subjects with at least 1 event; QM = once per month; SC = subcutaneous; TEAE = treatment-emergent adverse event.

- 6.29 In VANGUARD, 25 patients (64.1%) in the garadacimab arm and 15 patients (60.0%) in the placebo arm experienced at least one TEAE. The incidence of moderate TEAEs was higher in the garadacimab arm than in the placebo arm (41.0% vs. 28.0%). There was one severe TEAE occurred in one (2.6%) garadacimab-treated patient, but this event was considered not related to study treatment. No TEAEs caused death in either treatment arm.
- 6.30 Injection site reactions (ISRs) were reported in two (5.1%) garadacimab-treated patients and two (8.0%) placebo-treated patients. No patients in the study experienced an adverse event of special interest (AESI)<sup>6</sup>.
- 6.31 The most common AEs experienced by studied patients in VANGUARD were headache, upper respiratory tract infection, and nasopharyngitis. Of these, headache occurred more frequently in the placebo arm than in the garadacimab arm (16.0% vs. 7.7%). Conjunctivitis, sinusitis, urinary tract infection and abdominal pain occurred in patients treated with garadacimab only (5.1% for each AE), but not in the placebo group. On the contrary, fatigue (12.0%), nausea (8.0%), and pain in extremity (8.0%) were reported in patients receiving placebo, but not in the garadacimab group.
- 6.32 A total of 14 study treatment-related TEAEs were reported in VANGUARD. They were experienced by 4 patients (10.3%) in the garadacimab arm (9 events) and 3 patients (12.0%) in the placebo arm (5 events). All of the 5 treatment-related TEAEs in the placebo arm were mild adverse events (AEs). Among the 9 treatment-related TEAEs reported in the garadacimab arm, 4 were mild AEs and the remaining 5 were moderate AEs (all occurred in the same patient). No severe treatment-related TEAEs were reported in the trial. From the VANGUARD Clinical Study Report:
- all treatment-related TEAEs had an outcome of recovered or resolved, except for one (2.6%) patient in the garadacimab arm who experienced a mild event of prothrombin fragment 1.2 increase that had an outcome of not recovered or not resolved;
  - the most common study treatment-related TEAEs reported were ISRs and headache. Treatment-related ISRs occurred in 2 patients in each treatment arm (5.1% for garadacimab vs. 8.0% for placebo). The 5 treatment-related headache events were all with moderate severity, occurred in the same patient within 24 hours after SC dose and resolved within 2 to 3 days.
- 6.33 The evaluation considered that interpretation of the safety data from VANGUARD was hindered by the small number of patients in each treatment arm. It considered that the study was too small to identify rare AEs, such as AESIs which included thromboembolic events, bleeding events and severe hypersensitivity/anaphylaxis.

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<sup>6</sup> In VANGUARD, the following events were considered AESIs: thromboembolic events, bleeding events and severe hypersensitivity/anaphylaxis.

**Indirect comparison of garadacimab versus lanadelumab**

6.34 Table 8 and Table 9 summarise the results of the ITCs of TEAEs and serious AEs for garadacimab versus lanadelumab.

**Table 8: Indirect comparison of TEAEs during the treatment period in VANGUARD and HELP**

Trial ID	Comparison	Intervention n/N (%)	Placebo n/N (%)	OR (95% CI)	RR (95% CI)	RD (95% CI)
<b>GARA 200 QM vs LANA 300 Q2W</b>						
VANGUARD	GARA 200 QM vs Placebo	25/39 (64.1%)	15/25 (60.0%)	1.19 (0.42, 3.35)	1.07 (0.72, 1.59)	4.1% (-20.3%, 28.5%)
HELP	LANA 300 Q2W vs Placebo	26/27 (96.3%)	31/41 (75.6%)	8.39 (1.01, 69.92)	1.27 (1.05, 1.54)	20.7% (5.7%, 35.6%)
Indirect comparison	GARA 200 QM vs LANA 300 Q2W			0.14 (0.01, 1.5)	0.84 (0.54, 1.31)	-16.6% (-45.2%, 12.0%)
P-value	-			>0.05		
<b>GARA 200 QM vs LANA 300 Q4W</b>						
VANGUARD	GARA 200 QM vs Placebo	25/39 (64.1%)	15/25 (60.0%)	1.19 (0.42, 3.35)	1.07 (0.72, 1.59)	4.1% (-20.3%, 28.5%)
HELP	LANA 300 Q4W vs Placebo	25/29 (86.2%)	31/41 (75.6%)	2.02 (0.56, 7.21)	1.14 (0.91, 1.43)	10.6% (-7.6%, 28.8%)
Indirect comparison	GARA 200 QM vs LANA 300 Q4W			0.59 (0.11, 3.06)	0.94 (0.59, 1.48)	-6.5% (-36.9%, 23.9%)
P-value	-			>0.05		

Source: Table 2.53, p129 of the submission

CI = confidence interval; GARA = garadacimab; LANA = lanadelumab; N = number of patients in the treatment arm; n = number of patients experiencing at least 1 event; OR = odds ratio; QM = once per month; Q2W = once every 2 weeks; Q4W = once every 4 weeks; RD = risk difference; RR = relative risk; TEAE = treatment-emergent adverse event

Note: An indirect RD of < 0 or an indirect RR/OR of <1 indicates a result favouring garadacimab

**Table 9: Indirect comparison of the number of patients experiencing any serious adverse event during the treatment period in VANGUARD and HELP**

Trial ID	Comparison	Intervention n/N (%)	Placebo n/N (%)	Risk Difference (95% CI)
<b>GARA 200 QM vs LANA 300 Q2W</b>				
VANGUARD	GARA 200 QM vs Placebo	1/39 (2.6%)	0/25 (0.0%)	2.6% (-2.4%, 7.5%)
HELP	LANA 300 Q2W vs Placebo	1/27 (3.7%)	0/41 (0.0%)	3.7% (-3.4%, 10.8%)
Indirect comparison	GARA 200 QM vs LANA 300 Q2W			-1.1% (-9.8%, 7.5%)
P-value	-			>0.05
<b>GARA 200 QM vs LANA 300 Q4W</b>				
VANGUARD	GARA 200 QM vs Placebo	1/39 (2.6%)	0/25 (0.0%)	2.6% (-2.4%, 7.5%)
HELP	LANA 300 Q4W vs Placebo	3/29 (10.3%)	0/41 (0.0%)	10.3% (-0.7%, 21.4%)
Indirect comparison	GARA 200 QM vs LANA 300 Q4W			-7.8% (-19.9%, 4.4%)
P-value	-			>0.05

Source: Table 2.58, pp133-134 of the submission

CI = confidence interval; GARA = garadacimab; LANA = lanadelumab; N = number of patients in the treatment arm; n = number of patients experiencing at least 1 event; QM = once per month; Q2W = once every 2 weeks; Q4W = once every 4 weeks; RD = risk difference

Note: An indirect RD of < 0 indicates a result favouring garadacimab

6.35 For both TEAEs and serious AEs, results of the ITCs numerically favoured the garadacimab 200 mg QM regimen compared to the lanadelumab 300 mg Q2W and

Q4W regimens. However, the analyses of AE outcomes were not statistically powered, especially for the severe AEs and the overall low number of observed TEAEs and severe AEs further contributes to the uncertainty of the ITCs. In addition, safety results from the ITCs should be interpreted with consideration of the potential differences across the trials in terms of the patient characteristics at baseline.

## **Benefits/harms**

- 6.36 A benefits and harms table was not presented as the submission made a claim of non-inferiority.

## **Clinical claim**

- 6.37 The submission described garadacimab as non-inferior in terms of effectiveness compared to lanadelumab. The evaluation considered that this claim was uncertain and may not be supported by the evidence. The evaluation noted that although the 95% CIs of indirect estimates did not include a worsening of HAE attack outcomes which was clinically relevant to the proposed target population, the results should be interpreted with caution, given the following issues:

- The heterogeneity between the VANGUARD and HELP trials, and overall impact of the transitivity issues on the indirect results, which cannot be reliably estimated. However, the ESC considered that, given the similar event rates in the placebo arms of the trials (along with the additional subgroup analyses provided in the PSCR, which indicated that some of the differences in baseline characteristics between the trials were unlikely to be key treatment effect modifiers), the transitivity assumption was likely to have been upheld.
- The small number of patients in the VANGUARD and HELP trials and the inherent variability and unpredictability in HAE attack pattern and frequency. However, the ESC considered that the small patient numbers, and variability and unpredictability in HAE attacks is inherent in any study in HAE, given the rarity and characteristics of the condition.

- 6.38 The ESC considered that overall, the claim of non-inferior comparative effectiveness was likely to have been supported by the available evidence.

- 6.39 The submission described garadacimab as non-inferior in terms of safety compared to lanadelumab. The evaluation considered this claim was supported by the results of ITC for safety, but noted the following issues:

- The transitivity issues (noted above) due to the differences in patient baseline risks between the VANGUARD and HELP populations; and
- The VANGUARD trial and the ITC analyses were not sufficiently powered to reliability assess the comparative safety of garadacimab compared with placebo and with lanadelumab.

- Of note, long term efficacy and safety data for garadacimab was lacking (given the limited treatment duration in clinical studies), considering that therapy is likely to be ongoing in many HAE patients. The PSCR presented an additional data cut from VANGUARD as at June 2023 that indicated a continued treatment effect out to a median treatment duration of 1.6 years (to support the long-term efficacy of garadacimab). The ESC considered the claim of non-inferior comparative safety of garadacimab and lanadelumab was likely supported with the available evidence, noting the uncertainties due to small patient numbers and the lack of long-term follow-up data.

6.40 The PBAC considered that the claim of non-inferior comparative effectiveness and safety was adequately supported by the data.

### Economic analysis

6.41 The submission presented a CMA to support the listing of garadacimab for the prevention of HAE attacks. The key components and assumptions of the approach are presented in Table 10.

**Table 10: Key components and assumptions of the cost-minimisation approach presented in the submission**

Component	Claim or assumption
Therapeutic claim: effectiveness	Based on evidence presented, effectiveness is assumed to be non-inferior.
Therapeutic claim: safety	Based on evidence presented, safety is assumed to be non-inferior.
Evidence base	Indirect comparison of garadacimab (VANGUARD) and lanadelumab (HELP)
Equi-effective doses	Equi-effective dose in stabilised patients over a 1-year period: 12 doses of 200 mg garadacimab to 20 doses of 300 mg lanadelumab. The evaluation and the ESC considered this was not reasonable, as it excluded the loading dose. Further, as lanadelumab was only considered cost-effective at Q4W dosing, with an RSA to mitigate the risk of more frequent dosing (para 7.7, lanadelumab PSD, July 2021 PBAC meeting), it may be appropriate to cap the cost of lanadelumab to that based on Q4W dosing.
Direct medicine costs	The cost of garadacimab is higher per patient per year than lanadelumab, to account for a reduction in specialist attendances, described below.
Other costs or cost offsets	Consultant specialist attendances (to renew prescriptions) were assumed to reduce from 3.33 per year to 2 per year with garadacimab treatment. No differences in administration or significant differences were observed in the incidence (or profile) of AEs, so exclusion of these costs was reasonable.

Source: Constructed during the evaluation from Section 3 of the submission.

AE = adverse event; PSD = public summary document; Q4W = once every 4 weeks; RSA = risk sharing arrangement

6.42 The submission estimated the equi-effective doses in ongoing, stable patients as 12 doses of 200 mg garadacimab and 20 doses of 300 mg lanadelumab each year. This excluded the loading dose of garadacimab. The evaluation and the ESC noted that the PBAC had previously considered that, for drugs that include a loading dose in Year 1, the CMA should be conducted over a 2-year period from initiation of treatment (para 6.65 and 7.15, ravulizumab PSD, July 2021 PBAC meeting). The exclusion of the loading dose favoured garadacimab and the evaluation considered the loading dose should be included in the CMA. The PSCR maintained that it would be inappropriate to include the loading dose in a CMA over a two-year treatment period because this assumes

that stable, ongoing garadacimab patients will take an additional loading dose of garadacimab every second year they are on treatment. However, the ESC agreed with the evaluation that the CMA should include the garadacimab loading dose and should be calculated over 2 years, as per PBAC precedent for drugs that include a loading dose in Year 1, such as bDMARDs. The pre-PBAC response proposed that if the loading dose must be included, a 20-year treatment period would be preferable, as the loading dose is only once per lifetime; however, the PBAC considered that a 2-year period including a loading dose was appropriate, consistent with the approach taken for ravulizumab and bDMARDs.

- 6.43 The dose of garadacimab in ongoing, stable patients (once per month), was consistent with the draft PI and with use in the VANGUARD trial, where all patients randomised to garadacimab received all doses over the 6-month period, without dose adjustment. The evaluation considered that the assumption of full compliance with no dose adjustments may be reasonable, given that median compliance was 100% to the 200 mg garadacimab dose Q4W in the Phase 2 CSL312\_2001 trial, over an average exposure time of 546.1 days.
- 6.44 In the lanadelumab HELP trial, patients were randomised to receive either 300 mg lanadelumab Q2W or Q4W, with no up- or down-titration observed. The submission estimated the equi-effective dose of lanadelumab from a clinician survey (eight clinicians, representing 140 HAE patients) of the distribution of doses in practice in adequately-controlled patients (Q2W [i.e. 26.1 doses per year]: 44.4%; every three weeks [Q3W] [17.4 doses per year]: 9.3%; Q4W [13.0 doses per year]: 46.3%). However, the evaluation considered that given that garadacimab was claimed to be non-inferior to either the Q2W or Q4W dosing of lanadelumab, and given the difference in cost of the lanadelumab dosing regimens, it may be more appropriate for the CMA to be based on the 300 mg Q4W dose of lanadelumab alone. The evaluation noted that this approach would also be more consistent with the evidence presented to support the listing of lanadelumab, where lanadelumab was only considered cost-effective at the Q4W dosing, with a risk-sharing arrangement (RSA) to adequately mitigate the risk of expenditure exceeding the estimated financial impact based on Q4W dosing (para 7.7, lanadelumab PSD, July 2021 PBAC meeting). The PSCR maintained that it would be more appropriate to use mixed dosing, to reflect 'Australian clinical practice wherein 54% of lanadelumab patients are dosed more frequently than Q4W', and that the 'PBS would still pay double the annual lanadelumab treatment cost for Q2W patients compared to Q4W patients, until the subsidy cap is breached'. However, the ESC agreed with the evaluation that the CMA should compare garadacimab to lanadelumab Q4W, as that reflects the basis upon which the PBAC recommended that lanadelumab would be cost effective (paragraph 7.5, lanadelumab PSD, March 2021 PBAC meeting).
- 6.45 As garadacimab was associated with fewer scripts per year, the submission assumed a reduction in specialist attendances to obtain original scripts. However, the evaluation and the ESC considered that a reduction in specialist attendances due to

the introduction of garadacimab may not be realised as: prescribers can request an increase in the maximum quantity per script for patients receiving 300 mg lanadelumab Q2W (which would reduce the frequency of original scripts); and continuing treatment may be prescribed in consultation with a specialist allergist or clinical immunologist.

- 6.46 The results of the CMA presented in the submission are summarised in Table 11. The evaluation considered that given that the submission had overestimated the use of lanadelumab (as this has not been capped at Q4W dosing) and underestimated the use of garadacimab by not including the loading dose, the cost-minimised price for garadacimab was overestimated in the submission.

**Table 11: Results of the cost-minimisation approach presented in the submission (based on the published price of lanadelumab)**

	Parameter	Lanadelumab	Garadacimab	Source/calculation
<b>A</b>	<b>Total annual cost of treatment</b>	<b>\$369,083.17</b>	<b>\$369,083.17</b>	<b>Lanadelumab:</b> $A = G + J$ <b>Garadacimab:</b> $A$ (total annual garadacimab treatment costs = $A$ (total annual lanadelumab treatment costs))
<b>B</b>	Pack description	300 mg in 2 mL	200 mg in 1.2 mL	<b>Lanadelumab:</b> Approved lanadelumab TGA PI & lanadelumab PBS listing (PBS item code: 12790E) <b>Garadacimab:</b> Proposed garadacimab TGA PI
<b>C</b>	Administrations per pack	1	1	<b>Lanadelumab:</b> Lanadelumab PBS listing (PBS item code: 12790E) <b>Garadacimab:</b> Proposed garadacimab PBS restriction
<b>D</b>	No. of repeats	5	5	<b>Lanadelumab:</b> Lanadelumab PBS listing (PBS item code: 12790E) <b>Garadacimab:</b> Proposed garadacimab PBS restriction
<b>E</b>	No. administrations per patient per year	20.0	12.0	<b>Lanadelumab:</b> Weighted average number of annual lanadelumab doses calculated from Australian patients on long term, stable lanadelumab per Nov 2023 Advisory Board <b>Garadacimab:</b> Per proposed garadacimab TGA PI
<b>F</b>	<b>AEMP per administration<sup>a</sup></b>	<b>\$18,440.10</b>	<b>\$30,742.87</b>	<b>Lanadelumab:</b> Ex-manufacturer prices (excluding Efficient Funding of Chemotherapy) - 1 July 2024 <b>Garadacimab:</b> $(A - J) / (C \times E)$
<b>G</b>	Total annual drug costs	\$368,802.00	\$368,914.47	$G = F \times E$
<b>H</b>	Total annual clinician visits for prescription	3.33	2.00	$H = E / (C + D)$
<b>I</b>	Specialist visit MBS fee for prescription	\$84.35	\$84.35	MBS item code 116 reflecting prescribing by specialist allergist or clinical immunologist per lanadelumab PBS item code 1290E - continuing treatment phase restriction. Proposed garadacimab PBS continuing restriction reflects this treatment criteria.
<b>J</b>	Total annual specialist visit costs for prescription	\$281.17	\$168.70	$J = H \times I$

Source: Table 3-4, p146 of the submission

AEMP = approved ex-manufacturer price; PI = product information

<sup>a</sup> AEMP of lanadelumab reflects published AEMP. Effective lanadelumab AEMP is subject to special pricing arrangement.

6.47 The evaluation re-calculated the results of the CMA over the first 2 years following treatment initiation, with the cost of lanadelumab capped at Q4W dosing and accounting for the garadacimab loading dose (Table 12).

**Table 12: Results of the cost-minimisation approach, revised assuming lanadelumab cost capped at Q4W dosing, over 2 years from treatment initiation (based on the published price of lanadelumab)**

	Parameter	Lanadelumab	Garadacimab	Source/calculation
<b>A</b>	<b>Total cost over 2 years from treatment initiation</b>	<b>\$481,369.98</b>	<b>\$481,369.98</b>	<b>Lanadelumab:</b> $A = G + J$ <b>Garadacimab:</b> Lanadelumab cost over 2 years from treatment initiation
<b>B</b>	Pack description	300 mg in 2 mL	200 mg in 1.2 mL	<b>Lanadelumab:</b> PBS item 12790E <b>Garadacimab:</b> Draft garadacimab PI
<b>C</b>	Administrations per pack	1	1	<b>Lanadelumab:</b> PBS item 12790E <b>Garadacimab:</b> Proposed PBS restriction
<b>D</b>	No. of repeats	5	5	<b>Lanadelumab:</b> PBS item 12790E <b>Garadacimab:</b> Proposed PBS restriction
<b>E</b>	No. administrations over 2 years from treatment initiation	26.1	25.0	<b>Lanadelumab:</b> Cost capped at Q4W dosing <b>Garadacimab:</b> QM + 1 loading dose
<b>F</b>	<b>AEMP per administration <sup>a</sup></b>	<b>\$18,440.10</b>	<b>\$19,252.07</b>	<b>Lanadelumab:</b> AEMP, PBS item 12790E <b>Garadacimab:</b> $(A - J) / (C \times E)$
	<b>milligrams over 2 years from treatment initiation</b>	<b>7,821 mg</b>	<b>5,000 mg</b>	<b>Equi-effective doses over 2 years from treatment initiation</b>
<b>G</b>	Total drug cost over 2 years from treatment initiation	\$481,089.04	\$481,301.72	$G = E \times F$
<b>H</b>	No. specialist attendances for prescriptions over 2 years from treatment initiation	6.44	4.00	<b>Lanadelumab:</b> No. consultations required for prescriptions for each dose regimen, weighted by distribution of dose <b>Garadacimab:</b> $H = (E - 1) / (C + D)$
<b>I</b>	Specialist visit MBS fee for prescription	\$87.30	\$87.30	MBS item code 116 (current July 1 <sup>st</sup> , 2024)
<b>J</b>	Total cost of specialist attendances for prescriptions over 2 years from treatment initiation	\$561.88	\$349.20	$J = H \times I$

Source: Constructed during the evaluation from the 'Attachment 5 – Garadacimab CMA.xlsx' workbook included in the submission.

AEMP = approved ex-manufacturer price; PI = product information; Q4W = once every 4 weeks; QM = once per month

<sup>a</sup> AEMP of lanadelumab reflects published AEMP. Effective lanadelumab AEMP is subject to special pricing arrangement.

### Drug cost/patient/year

6.48 Based on the published price of lanadelumab, the cost per patient per year for:

- garadacimab would be \$370,866, estimated from the cost-minimised dispensed price for maximum quantity (DPMQ) (\$30,905.47 per script), assuming 12 garadacimab scripts per patient per year (as assumed in the CMA presented in the submission).
- lanadelumab was \$372,054, based on the published DPMQ (\$18,602.70), assuming 20 scripts per patient per year.

## Estimated PBS usage & financial implications

6.49 This submission was considered by DUSC.

6.50 The submission presented a market-share approach to estimate the use and financial implications for listing garadacimab for the prevention of HAE attacks. A summary of the data sources and parameter values used is presented in Table 13.

**Table 13: Key inputs for financial estimates**

Parameter	Value applied and source	Comment
Size of market for HAE mAb prophylaxis in year prior to listing	1,434 based on PBS item statistics for lanadelumab (12790E), May 2023 – April 2024	This was reasonable.
Population growth	2.2% (assumed)	The evaluation considered that this was not appropriate as the ABS projects lower population growth (1.6% in those aged ≥12 years). DUSC and PBAC considered this to be an overestimate and considered a growth rate in the range of 1.2-1.6% to be more reasonable (see paragraph 6.51)
Number of patients who switch from C1-INH prophylaxis	Year 1: █████ <sup>1</sup> ; Year 2: █████; Year 3: █████ <sup>1</sup> ; Year 4: █████ <sup>1</sup> ; Year 5: █████ <sup>1</sup> ; Year 6: █████ <sup>1</sup> Calculated from the submission's estimate of: (a) the number of C1-INH patients (75 in Year 1 decreasing to █████ <sup>1</sup> in Year 6, estimated from the sponsor-supported Nursecare Program); (b) who switch each year, assuming that 10% of patients on C1-INH prophylaxis switch each year.	The number of patients on C1-INH was assumed to be stable; changes each year were due only to switching to mAb prophylaxis. The PSCR and DUSC noted there was an error in the calculations and the number of patients on C1-INH should be █████ <sup>1</sup> in Year 1 based on the submission's methods.
Market growth due to patients switching from C1-INH	Year 1: █████%; Year 2: █████%; Year 3: █████%; Year 4: █████%; Year 5: █████%; Year 6: █████% Calculated by dividing the numbers in the row above by the estimated number patients treated with lanadelumab (the submission estimated that █████ <sup>1</sup> patients are currently on lanadelumab treatment, based on the average number of scripts per month, April–May 2024 (128.5), assuming 1.67 scripts (20 ÷ 12) per patient)	The evaluation and DUSC considered that this may be inaccurate due to the conversion of the number of scripts into patient numbers, which was then used to derive an estimate that would be applied to script numbers. The PBAC advised that the submission's method for estimating market growth due to patients switching from C1-INH was likely reliable but should be corrected for the issues identified by DUSC (including the error outlined in the row above).
Uptake rate	█████% in Year 1, increasing to █████% by Year 5 (assumed)	The evaluation considered that the basis for this was unclear, and given the assumed high proportion of patients currently treated with lanadelumab Q2W or Q3W, uptake may be higher in initial years. However, DUSC and PBAC considered that while this estimate was uncertain, it may be reasonable.
Garadacimab substitution rate of lanadelumab scripts	Initial: 1.2; Continuing: 0.6 Based on garadacimab use of 2 scripts in the first month, 1 script per month thereafter; and lanadelumab use of 1.67 scripts per month (assuming 20 scripts per year, based on the CMA)	As the submission proposed a separate item for the initial script (which covers both doses), this approach overestimated the number of initial scripts. DUSC noted the uncertainty in script substitution but considered the estimates for the number of scripts may be reasonable, noting the significant impact of small changes in these assumptions on treatment costs.

Parameter	Value applied and source	Comment
Proportion of garadacimab scripts that are initial scripts	Year 1: █%; Year 2: █%; Year 3: █%; Year 4: █%; Year 5: █%; Year 6: █%  Derived from the proportion of initial scripts assuming █ <sup>1</sup> patients are currently treated with lanadelumab, who uptake garadacimab █–█% over Years 1–6	The evaluation considered that this approach was not justified, was not consistent with other assumptions applied and was implemented erroneously. Overall, the PBAC advised that, where possible, the financial estimates should be updated to be based on patient-level PBS data.
Grandfathered patients	█ <sup>1</sup> based on the number of Australian patients enrolled in the garadacimab open-label extension study.	The estimated number of patients was reasonable, however garadacimab use was not quantified in these patients. The PBAC considered that it may be reasonable to include the grandfather patients in the financial in the financial estimates given the market share approach and the relatively low uptake assumed in Year 1.

Source: Table 4.1, p149 of the submission.

ABS = Australian Bureau of Statistics; C1-INH = C1-esterase inhibitor; CMA = cost-minimisation approach; HAE = hereditary angioedema; mAb = monoclonal antibody; Q2W = once every 2 weeks; Q3W = once every 3 weeks

The redacted values correspond to the following ranges:

<sup>1</sup> < 500

- 6.51 As lanadelumab is currently the only monoclonal antibody (mAb) listed on the PBS for the prophylactic treatment of HAE, the submission estimated the size of the current market based on the number of lanadelumab scripts dispensed (PBS item 12790E), over the 12-month period, May 2023 – April 2024. The evaluation considered this was reasonable. To project estimates over the first 6 years of listing, the submission applied a 2.2% growth rate, assumed to represent population growth. However, DUSC and PBAC considered this was an overestimate, with a more likely estimate to be in the range of 1.2% (based on Pharmaceutical Benefits Scheme (PBS) script numbers) to 1.6% (based on Australian Bureau of Statistics (ABS) projections for the population aged 12+).
- 6.52 In addition to population growth, the submission assumed that the introduction of garadacimab would grow the market for monoclonal antibody (mAb) prophylaxis due to patients switching from prophylactic C1-INH. The submission noted that there had been some switching from lanadelumab back to (subcutaneous) C1-INH due to efficacy concerns and injection site pain in Australian clinical practice. DUSC agreed that, while a significant proportion of patients had already transitioned from C1-INH to lanadelumab, there had been some small movement back to C1-INH due to side-effects experienced with lanadelumab. The PBAC considered that, with the listing of garadacimab, there may be a small increase to the size of the market for mAb prophylaxis as it is likely that some patients may have trialled lanadelumab but switched back to subcutaneous C1-INH due to tolerability concerns.
- 6.53 The evaluation and DUSC considered that there may have been inaccuracies in the submission’s method for estimating market growth due to patients switching from C1-INH because: the basis for the number of patients on prophylactic C1-INH was not well described; the calculation included an error (the number of patients on C1-INH should be < 500 in Year 1 based on the submission’s methods); and patient numbers were

estimated from script numbers, with the derived patient numbers then being used to determine script volumes. DUSC stated that, alternatively, these patients could have been included separately, with estimates of use then applied.

- 6.54 The submission assumed that the uptake of garadacimab would increase from  $\frac{1}{2}$ % in Year 1, to  $\frac{1}{2}$ % in Year 5. The evaluation considered that uptake may be higher in initial years given the high proportion of patients currently treated with lanadelumab Q2W or Q3W (53%, based on a survey of clinicians) and if patients switching from C1-INH would preferentially receive garadacimab e.g. due to its dosing profile. Overall, DUSC and PBAC considered that the submission's estimated uptake rate, while uncertain, may be reasonable
- 6.55 The commentary and DUSC considered that the method used to estimate the proportion of initial garadacimab scripts (which require a loading dose) had inherent inaccuracies due to:
- the number of patients was not assumed to change over time, which was not consistent with growth estimates applied elsewhere in the financial estimates; and
  - the conversion from scripts to patient numbers, which was required because the submission did not have access to patient-level data. An analysis conducted by the DUSC Secretariat found the number of initiating lanadelumab patients was higher than estimated in the submission.
- 6.56 DUSC considered that the use of PBS data could be considered to better estimate dosing and script equivalencies between lanadelumab and garadacimab. The PBAC agreed and advised that, where possible, the financial estimates should be updated to be based on patient-level PBS data.
- 6.57 DUSC considered that there was scope for the market for mAb prophylaxis to grow beyond the level estimated (e.g. due to patients who are not currently on prophylaxis) and potential for use outside the restriction in patients with less severe disease due to the subjective nature of what constitutes a HAE attack. However, the pre-PBAC response argued that attacks requiring acute treatment are not ambiguous as these are determined by severity and clinical need. Overall, the PBAC considered these issues were adequately addressed given the requirement for a written Authority for initial treatment and the RSA.
- 6.58 The proposed PBS listing for garadacimab was expected to result in a decrease in the use of lanadelumab. No changes to the utilisation of other PBS-listed medicines were expected to arise from the inclusion of garadacimab on the PBS.
- 6.59 The submission's estimates for the number of patients treated and financial impact of garadacimab over the first 6 years of listing is presented in Table 14.

**Table 14: Estimated use and financial implications**

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Growth in lanadelumab scripts, due to population growth	2.2%	2.2%	2.2%	2.2%	2.2%	2.2%
Growth in lanadelumab scripts, due to switching from C1-INH	█%	█%	█%	█%	█%	█%
Projected lanadelumab market <sup>a,b</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>
Garadacimab market share	█%	█%	█%	█%	█%	█%
Reduction in lanadelumab scripts [A]	█ <sup>2</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>
Proportion of garadacimab scripts that are initial [B]	█%	█%	█%	█%	█%	█%
<b>No garadacimab scripts</b>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>
• Initial [A × B × 1.2]	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>
• Continuing [A × (1 – B) × 0.6]	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>
Cost of garadacimab to the PBS/RPBS, less patient copayments <sup>c</sup>	█ <sup>3</sup>	█ <sup>4</sup>	█ <sup>5</sup>	█ <sup>5</sup>	█ <sup>6</sup>	█ <sup>6</sup>
Reduction in cost of lanadelumab to the PBS/RPBS, less patient copayments <sup>d</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>4</sup>	█ <sup>4</sup>	█ <sup>5</sup>	█ <sup>5</sup>
<b>Net cost to the PBS/RPBS</b>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>4</sup>	█ <sup>4</sup>

Source: '2e. Scripts – market' and '3a. Scripts – proposed' worksheet of the 'Attachment 14 - Garadacimab utilisation and cost workbook.xlsx' included in the submission and Table 4.10, p156 of the submission.

C1-INH = C1-esterase inhibitor

<sup>a</sup> Assuming 1,434 lanadelumab scripts in the year prior to listing, based on utilisation of PBS item 12790E, over the 12-month period, May 2023 – April 2024

<sup>b</sup> Scripts in the previous year multiplied by (1 + population growth + growth due to switching from C1-INH), so in 2025 this was estimated from  $1,434 \times (1 + 0.022 + 0.097)$

<sup>c</sup> \$ █ per script

<sup>d</sup> \$ █ per script

The redacted values correspond to the following ranges:

1 500 to < 5,000

2 < 500

3 \$0 to < \$10 million

4 \$10 million to < \$20 million

5 \$20 million to < \$30 million

6 \$30 million to < \$40 million

6.60 As the estimates were presented based on proposed published pricing of garadacimab (based on cost-minimisation to the Q2W dosing of lanadelumab), net costs to the PBS/RPBS were estimated to be \$10 million to < \$20 million in Year 6, and a total of \$40 million to < \$50 million in the first 6 years of listing. The submission stated that the estimated net financial implication would be expected to be neutral if the effective prices were applied.

6.61 The submission assumed that the listing of garadacimab would result in no changes to the use and cost of MBS items. While this was not consistent with the reduction in

specialist attendances (from 3.3 to 2.0 per patient per year) assumed in the submission's CMA, the PBAC considered that the claimed reduction may not be realised (as described in paragraph 6.45).

- 6.62 While not explicitly calculated, the submission considered that there would also be savings to the health system due to patients who switch from C1-INH (which is currently accessed through the NBA). The evaluation noted that a reduction in these costs would only occur if these patients would not otherwise have switched to lanadelumab.

### **Quality use of Medicines**

- 6.63 DUSC considered that there was some potential for discontinuation and episodic use, and that associated risks and management of flares could be considered in any education material.
- 6.64 DUSC noted differences in the refrigeration requirements of lanadelumab compared to garadacimab in that garadacimab can be stored outside for longer, and considered that the sponsor could highlight these differences in educational material, for the awareness of patients switching between products.

### **Financial Management – Risk Sharing Arrangements**

- 6.65 The submission noted that lanadelumab is subject to an RSA. The evaluation and the ESC noted that the RSA was established for the following three reasons:
- to account for the risk of patients receiving more than 13 lanadelumab injections per year (given lanadelumab can be administered Q2W or Q4W);
  - to manage the risk of use in cost-ineffective populations, notably the risk of use in patients who experience  $\leq 24$  attacks per year; and
  - to achieve cost-effectiveness, i.e. to achieve the price at which the PBAC had considered lanadelumab would represent an acceptable level of cost-effectiveness in those patients who switch from SoC (Paragraphs 6.29, 6.57 and 6.58, Lanadelumab Minutes, July 2021 PBAC Meeting).
- 6.66 The evaluation and the ESC agreed with the submission that the risk of more frequent lanadelumab dosing would not be relevant for garadacimab which is administered as a fixed once-monthly dosing regimen. Thus, the ESC considered that the sponsor of garadacimab should not be adversely affected by the risks associated with the uncertain lanadelumab dosing frequency.
- 6.67 However, the evaluation and the ESC considered that both of the other risks would be relevant to garadacimab and would need to be managed through an RSA.
- 6.68 The ESC advised that a combined RSA expenditure cap would be appropriate given garadacimab is expected to replace lanadelumab (and listing was sought on a cost-minimisation basis), consistent with usual practice. In addition, as the lanadelumab RSA is required to achieve a particular level of cost-effectiveness, a joint RSA

expenditure cap would help ensure an equivalent level of cost-effectiveness for both items.

- 6.69 The pre-PBAC response reiterated concerns regarding garadacimab joining the lanadelumab RSA, particularly if garadacimab is cost-minimised to lanadelumab Q4W without considering the dosing frequency used in Australian clinical practice. The pre-PBAC response stated that, under a combined RSA with annual treatment costs based on lanadelumab Q4W, lanadelumab would “disproportionally consume more of the cap, as 54% of stabilised lanadelumab patients are on a Q2W dosing regimen.” The pre-PBAC response argued that “the most practical method to cost minimise garadacimab to lanadelumab is to use the approach described in the submission which accurately calculates the equi-effective dose by considering dose mix informed by actual PBS-funded lanadelumab use in the Australian clinical setting, including the proportion of lanadelumab patients on Q2W, Q3W and Q4W treatment regimens.” The PBAC noted these concerns and advised that a combined RSA expenditure cap would be appropriate but considered that the sponsor of garadacimab should not be adversely affected by more frequent lanadelumab dosing.
- 6.70 Additionally, the ESC considered that some patients currently on C1-INH, who would not otherwise be treated with lanadelumab (e.g. due to adverse effects) may switch to garadacimab, and therefore a small increase in the RSA expenditure cap may be reasonable (refer to paragraph 6.52 and 6.53).

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

## **7 PBAC Outcome**

- 7.1 The PBAC recommended the General Schedule, Authority Required listing of garadacimab for the prophylaxis of recurrent attacks of hereditary angioedema (HAE) Types I and II. The PBAC’s recommendation for listing was based on, among other matters, its assessment that the cost-effectiveness of garadacimab would be acceptable if it were cost-minimised against lanadelumab. The PBAC advised that garadacimab should join the existing lanadelumab RSA with a small increase in expenditure caps due to switching of patients from C1-INH who would not otherwise be treated with lanadelumab.
- 7.2 The PBAC noted and welcomed the input from individuals, health professionals and organisations via the Consumer Comments facility. The PBAC noted that the comments highlighted the variable individual responses and tolerability to existing treatments, along with the advantages that garadacimab may have given the potential for self-administration and less frequent dosing. Overall, the comments outlined that the availability of garadacimab would provide a valuable alternative therapy for patients.
- 7.3 The PBAC considered that the nominated comparator of lanadelumab was appropriate.

- 7.4 The PBAC noted the submission was supported by one randomised controlled trial (RCT) that compared garadacimab with placebo (VANGUARD). The submission's claim of non-inferior comparative effectiveness and safety was based on an indirect comparison between the VANGUARD trial and the key trial of lanadelumab versus placebo (HELP). The PBAC noted the trials were small, which added uncertainty to the analyses, but acknowledged that HAE is a rare condition. The PBAC considered that the VANGUARD and HELP trials were sufficiently similar to enable a reliable indirect comparison, noting the similar event rates in the placebo arms of the trials.
- 7.5 The PBAC noted that there was no statistically significant difference in the comparison between garadacimab and either 2-weekly or 4-weekly lanadelumab in terms of the number of time-normalised HAE attacks, HAE attacks requiring on-demand treatment and moderate/severe HAE attacks, acknowledging the wide confidence intervals. The PBAC considered that the claim of non-inferior comparative effectiveness and safety versus lanadelumab was adequately supported based on the available data.
- 7.6 The PBAC therefore considered that listing on a cost-minimisation basis versus lanadelumab was reasonable. The PBAC considered that the cost-minimisation approach (CMA) should be conducted over a 2-year period from the initiation of treatment and should include the garadacimab loading dose, consistent with the approach used for other on-going chronic therapies that require a loading dose. The PBAC further considered that a reduction in specialist attendances should not be included in the CMA because: prescribers can request an increase in the maximum quantity per script; and continuing treatment may be prescribed by general practitioners in consultation with a specialist allergist or clinical immunologist.
- 7.7 The PBAC considered the equi-effective doses over 2 years from treatment initiation to be: garadacimab 5,000 mg and lanadelumab 7,821 mg.
- 7.8 The PBAC noted that lanadelumab was recommended for listing based on acceptable cost-effectiveness assuming Q4W dosing; however in practice, lanadelumab appears to be used more frequently by a substantial proportion of patients (with the submission estimating that the lanadelumab dosing frequency in clinical practice is: 44.4% Q2W; 9.3% Q3W; and 46.3% Q4W, based on a clinician survey). The PBAC advised that the sponsor and Department may consider the actual lanadelumab dosing frequency in clinical practice, in the context of garadacimab joining the existing RSA (refer to paragraph 7.10) while ensuring that the cost of garadacimab is no higher than lanadelumab.
- 7.9 The PBAC considered that the submission's market-share approach to estimating utilisation was reasonable and advised that, where possible, the financial estimates should be updated to be based on patient-level PBS data.
- 7.10 The PBAC noted that lanadelumab is subject to an RSA, which is intended to: (a) account for the risk of higher dosing frequency; (b) manage the risk of use in cost-ineffective populations; and (c) achieve cost-effectiveness for the listing. The PBAC considered that the risk of a higher dosing frequency was not relevant to garadacimab,

but that the other risks are relevant and should be managed within an RSA. The PBAC advised that garadacimab should join the existing lanadelumab RSA expenditure cap given: garadacimab is expected to replace lanadelumab; and the RSA is required to achieve a particular level of cost-effectiveness. However, the PBAC further advised that the sponsor of garadacimab should not be adversely affected by the risk of more frequent lanadelumab dosing.

- 7.11 The PBAC considered a small increase in tier 1 of the combined RSA expenditure threshold may be reasonable as there may be some patients who are currently treated with C1-INH who may switch to garadacimab (i.e. to account for patients who may have trialled lanadelumab but switched back to subcutaneous C1-INH due to tolerability). The PBAC advised that the submission's method for estimating market growth due to patients switching from C1-INH was likely reliable but should be corrected for the issues identified by DUSC (refer to paragraph 6.53).
- 7.12 The PBAC advised that it would be appropriate to align the garadacimab listings with the existing listings for lanadelumab, noting the need for an additional switching restriction and a grandfather restriction. The PBAC noted that the submission proposed inclusion of a criteria requiring a patient to be aged 12 years or older to access garadacimab, but advised that it would be appropriate for the listing to be age-agnostic.
- 7.13 The PBAC advised that the initial restrictions (initial and balance of supply restrictions) for garadacimab should provide up to six months of treatment (including the loading dose), consistent with the lanadelumab restriction. This would allow sufficient time for a patient to demonstrate an adequate response to treatment.
- 7.14 The PBAC advised that flow-on changes would be required to the lanadelumab restriction to allow switching from garadacimab to lanadelumab and to prevent combination use with garadacimab.
- 7.15 The PBAC recommended that garadacimab and lanadelumab should be treated as interchangeable, according to s101(3BA) advice.
- 7.16 The PBAC advised that garadacimab is not suitable for prescribing by nurse practitioners.
- 7.17 The PBAC advised that garadacimab should not be exempt from the Early Supply Rule as it currently applies to lanadelumab.
- 7.18 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because garadacimab is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over lanadelumab, or not expected to address a high and urgent unmet clinical need given the presence of an alternative therapy, the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were not met.

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

**Outcome:**

Recommended

## 8 Recommended listing

8.1 Add new item:

Name, Restriction, Manner of administration and form	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Proprietary Manufacturer	Name and
GARADACIMAB  garadacimab 200 mg/1.2 mL injection, 1.2 mL pen device	NEW	2	2	0	ANDEMBR Y	CSL Behring (Australia) Pty Ltd

**Restriction Summary: Based on 12464 / Treatment of Concept: 12464 (additional initial (switch) restriction, balance of supply, Grandfather and continuing restrictions separate due to loading dose for initiation).**

<b>Category / Program:</b> GENERAL – General Schedule (Code GE)
<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners
<b>Restriction Level / Method:</b> <input checked="" type="checkbox"/> Authority Required ((Full assessment) in writing only via post/HPOS upload)
<b>Administrative Advice:</b> No increase in the maximum quantity or number of units may be authorised.
<b>Administrative Advice:</b> No increase in the maximum number of repeats may be authorised.
<b>Administrative Advice:</b> Special Pricing Arrangements Apply
<b>Indication:</b> Chronic treatment of hereditary angioedema Types 1 or 2
<b>Treatment Phase:</b> Initial 1: New patient (commencing with no previous treatment with C1-INH for routine prophylaxis)
<b>Clinical criteria:</b>
Patient must have experienced at least 12 treated acute attacks of hereditary angioedema within the 6 month period prior to commencing treatment with this drug
<b>AND</b>
<b>Clinical criteria:</b>
Patient must not have been receiving a C1-esterase inhibitor through the National Blood Authority as routine prophylaxis for hereditary angioedema at the time of application
<b>AND</b>
<b>Clinical criteria:</b>
The treatment must not be used in combination with either: (i) a C1-esterase inhibitor concentrate (ii) lanadelumab
<b>AND</b>
<b>Treatment criteria:</b>
Must be treated by a clinical immunologist or a specialist allergist
<b>Prescribing Instructions:</b> For the purposes of administering this restriction, acute attacks of hereditary angioedema are those of a severity necessitating immediate medical intervention with either (i) icatibant, or (ii) C1-esterase inhibitor concentrate

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	<b>Prescribing Instructions:</b> The baseline measurement of the number of treated acute attacks of hereditary angioedema within the 6 months prior to initiating treatment must be provided at the time of submitting this application.
	<b>Administrative Advice:</b> Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at <a href="http://www.servicesaustralia.gov.au">www.servicesaustralia.gov.au</a> Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at <a href="http://www.servicesaustralia.gov.au/hpos">www.servicesaustralia.gov.au/hpos</a> Or mailed to: Services Australia Complex Drugs Reply Paid 9826 HOBART TAS 7001

	<b>Indication:</b> Chronic treatment of hereditary angioedema Types 1 or 2
	<b>Treatment Phase:</b> Initial 2: New patient (commencing from National Blood Authority-funded C1-INH)
	<b>Clinical criteria:</b>
	Patient must have been receiving a C1-esterase inhibitor through the National Blood Authority as routine prophylaxis for hereditary angioedema immediately prior to receiving this drug
	<b>AND</b>
	<b>Clinical criteria:</b>
	The treatment must not be used in combination with either: (i) a C1-esterase inhibitor concentrate or (ii) lanadelumab
	<b>AND</b>
	<b>Treatment criteria:</b>
	Must be treated by a clinical immunologist or a specialist allergist
	<b>Administrative Advice:</b> Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at <a href="http://www.servicesaustralia.gov.au">www.servicesaustralia.gov.au</a> Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at <a href="http://www.servicesaustralia.gov.au/hpos">www.servicesaustralia.gov.au/hpos</a> Or mailed to: Services Australia Complex Drugs Reply Paid 9826 HOBART TAS 7001

	<b>Indication:</b> Chronic treatment of hereditary angioedema Types 1 or 2
	<b>Treatment Phase:</b> Initial 3: New patient (transitioning from PBS-subsidised lanadelumab)
	<b>Clinical criteria:</b>
	Patient must have been receiving lanadelumab through the PBS as routine prophylaxis for hereditary angioedema immediately prior to receiving this drug.
	<b>AND</b>
	<b>Clinical criteria:</b>
	The treatment must not be used in combination with either: (i) a C1-esterase inhibitor concentrate (ii) lanadelumab
	<b>AND</b>

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<b>Treatment criteria:</b>
Must be treated by a clinical immunologist or a specialist allergist
<b>Administrative Advice:</b> Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at <a href="http://www.servicesaustralia.gov.au">www.servicesaustralia.gov.au</a> Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at <a href="http://www.servicesaustralia.gov.au/hpos">www.servicesaustralia.gov.au/hpos</a> Or mailed to: Services Australia Complex Drugs Reply Paid 9826 HOBART TAS 7001

Name, Restriction, Manner of administration and form	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Proprietary Name and Manufacturer
GARADACIMAB  garadacimab 200 mg/1.2 mL injection, 1.2 mL pen device	NEW	1	1	4	ANDEMBRY  CSL Behring (Australia) Pty Ltd

**Restriction Summary: Based on (new1) / Treatment of Concept: (new1A)**

<b>Concept ID</b>	<b>Category / Program:</b> GENERAL – General Schedule (Code GE)
	<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners
	<b>Restriction Level / Method:</b> <input checked="" type="checkbox"/> Authority Required – (immediate assessment) telephone/online
	<b>Administrative Advice:</b> No increase in the maximum quantity or number of units may be authorised.
	<b>Administrative Advice:</b> No increase in the maximum number of repeats may be authorised.
	<b>Administrative Advice:</b> Special Pricing Arrangements Apply
	<b>Indication:</b> Chronic treatment of hereditary angioedema Types 1 or 2
	<b>Treatment Phase:</b> Initial 1: New patient (commencing with no previous treatment with C1-INH for routine prophylaxis), Initial 2: New patient (commencing from National Blood Authority-funded C1-INH) or Initial 3: New patient (transitioning from PBS-subsidised lanadelumab) – balance of supply
	<b>Clinical criteria:</b>
	Patient must have received insufficient therapy with this drug for this condition under the Initial 1: New patient (commencing with no previous treatment with C1-INH for routine prophylaxis) restriction to complete 24 weeks treatment; OR
	Patient must have received insufficient therapy with this drug for this condition under the Initial 2: New patient (commencing from National Blood Authority-funded C1-INH) restriction to complete 24 weeks treatment; OR
	Patient must have received insufficient therapy with this drug for this condition under the Initial 3: New patient (transitioning from PBS-subsidised lanadelumab) restriction to complete 24 weeks treatment
	<b>AND</b>
	<b>Clinical criteria:</b>
	The treatment must provide no more than the balance of up to 24 weeks treatment available under the above restriction.

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<b>Clinical criteria:</b>
The treatment must not be used in combination with either: (i) a C1-esterase inhibitor concentrate (ii) lanadelumab
<b>AND</b>
<b>Treatment criteria:</b>
Must be treated by a specialist allergist or clinical immunologist, or in consultation with a specialist allergist or clinical immunologist
<b>Prescribing Instructions:</b> For the purposes of administering this restriction, an adequate response is a reduction of the baseline number of acute attacks of hereditary angioedema of a severity necessitating immediate medical intervention with either (i) icatibant, or (ii) C1-esterase inhibitor concentrate. The details of the reduction must be documented in the patient's medical records for auditing purposes.
<b>Administrative Advice:</b> Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see <a href="http://www.servicesaustralia.gov.au/HPOS">www.servicesaustralia.gov.au/HPOS</a> ) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).

Name, Restriction, Manner of administration and form	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Proprietary Name and Manufacturer
GARADACIMAB garadacimab 200 mg/1.2 mL injection, 1.2 mL pen device	NEW	1	1	5	ANDEMBRY CSL Behring (Australia) Pty Ltd

**Restriction Summary: Based on 12464 / Treatment of Concept: 12464 (additional initial (switch) restriction. Grandfather and continuing restrictions separate due to loading dose for initiation).**

<b>Concept ID</b>	<b>Category / Program:</b> GENERAL – General Schedule (Code GE)
	<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners
	<b>Restriction Level / Method:</b> <input checked="" type="checkbox"/> Authority Required – (immediate assessment) telephone/online
	<b>Administrative Advice:</b> No increase in the maximum quantity or number of units may be authorised.
	<b>Administrative Advice:</b> No increase in the maximum number of repeats may be authorised.
	<b>Administrative Advice:</b> Special Pricing Arrangements Apply
	<b>Indication:</b> Chronic treatment of hereditary angioedema Types 1 or 2
	<b>Treatment Phase:</b> Continuing preventative treatment
	<b>Clinical criteria:</b>
	Patient must have previously received PBS-subsidised treatment with this drug for this condition
	<b>AND</b>
	<b>Clinical criteria:</b>
	Patient must have demonstrated or sustained an adequate response to PBS-subsidised treatment with this drug for this condition
	<b>AND</b>
	<b>Clinical criteria:</b>
	The treatment must not be used in combination with either: (i) a C1-esterase inhibitor concentrate (ii) lanadelumab
	<b>AND</b>
	<b>Treatment criteria:</b>

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	Must be treated by a specialist allergist or clinical immunologist, or in consultation with a specialist allergist or clinical immunologist
	<b>Prescribing Instructions:</b> For the purposes of administering this restriction, an adequate response is a reduction of the baseline number of acute attacks of hereditary angioedema of a severity necessitating immediate medical intervention with either (i) icatibant, or (ii) C1-esterase inhibitor concentrate. The details of the reduction must be documented in the patient's medical records for auditing purposes.
	<b>Administrative Advice:</b> Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).

Name, Restriction, Manner of administration and form	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Proprietary Manufacturer	Name and
GARADACIMAB  garadacimab 200 mg/1.2 mL injection, 1.2 mL pen device	NEW	1	1	5	ANDEM BR Y	CSL Behring (Australia) Pty Ltd

**Restriction Summary: New – Based on [new2] / Treatment of Concept: [new2A] Grandfather restriction**

<b>Concept ID</b>	<b>Category / Program:</b> GENERAL – General Schedule (Code GE)
	<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners
	<b>Restriction Level / Method:</b> <input checked="" type="checkbox"/> Authority Required – ((Full assessment) in writing only via post/HPOS upload)
	<b>Administrative Advice:</b> No increase in the maximum quantity or number of units may be authorised.
	<b>Administrative Advice:</b> No increase in the maximum number of repeats may be authorised.
	<b>Administrative Advice:</b> Special Pricing Arrangements Apply
	<b>Indication:</b> Chronic treatment of hereditary angioedema Types 1 or 2
	<b>Treatment Phase:</b> Transitioning from non-PBS to PBS-subsidised treatment– Grandfather arrangements
	<b>Clinical criteria:</b>
Placeholder	Patient must have received non-PBS subsidised treatment with this drug for this condition as routine prophylaxis for hereditary angioedema prior to [listing date],
	<b>AND</b>
	<b>Clinical criteria:</b>
	Patient must have experienced at least 12 treated acute attacks of hereditary angioedema within the 6 month period prior to commencing non-PBS subsidised treatment with this drug for this condition; OR
	Patient must have been receiving a C1-esterase inhibitor through the National Blood Authority as routine prophylaxis for hereditary angioedema immediately prior to receiving non-PBS subsidised treatment with this drug for this condition;
	<b>AND</b>
	<b>Clinical criteria:</b>
	The treatment must not be used in combination with either: (i) a C1-esterase inhibitor concentrate or (ii) lanadelumab
	<b>AND</b>
	<b>Treatment criteria:</b>
	Must be treated by a specialist allergist or clinical immunologist, or in consultation with a specialist allergist or clinical immunologist

	<b>Prescribing Instructions:</b> For the purposes of administering this restriction, acute attacks of hereditary angioedema are those of a severity necessitating immediate medical intervention with either (i) icatibant, or (ii) C1-esterase inhibitor concentrate
	<b>Prescribing Instructions:</b> The baseline measurement of the number of treated acute attacks of hereditary angioedema within the 6 months prior to initiating non-PBS subsidised treatment must be provided at the time of submitting this application.
	<b>Prescribing Instructions:</b> For the purposes of administering this restriction, an adequate response is a reduction of the baseline number of acute attacks of hereditary angioedema of a severity necessitating immediate medical intervention with either (i) icatibant, or (ii) C1-esterase inhibitor concentrate. The details of the reduction must be documented in the patient's medical records for auditing purposes.
	<b>Administrative advice:</b> This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria.
	<b>Administrative advice:</b> Patients may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a 'Grandfathered' patient must qualify under the 'Continuing treatment' criteria.
	<b>Administrative Advice:</b> Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at <a href="http://www.servicesaustralia.gov.au">www.servicesaustralia.gov.au</a> Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at <a href="http://www.servicesaustralia.gov.au/hpos">www.servicesaustralia.gov.au/hpos</a> Or mailed to: Services Australia Complex Drugs Reply Paid 9826 HOBART TAS 7001

HPOS = Health Professional Online Services; PBS = Pharmaceutical Benefits Scheme

### Flow on changes

- 8.2 Amend initial 1: New patient (commencing with no previous treatment with C1-INH for routine prophylaxis), Initial 2: New patient (commencing from National Blood Authority-funded C1-INH) and continuing treatment phase for Lanadelumab ([12790E](#)) as follows:

	The treatment must not be <del>PBS-subsidised in combination with a C1-esterase inhibitor concentrate</del> used in combination with either: (i) a C1-esterase inhibitor concentrate (ii) lanadelumab
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- 8.3 New listing to allow switching from PBS-subsidised garadacimab to lanadelumab

Initial treatment – New patient transitioning from PBS-subsidised Garadacimab to lanadelumab

Restriction Summary New[3]/ ToC: New [3A]

	<b>Category / Program:</b> GENERAL – General Schedule (Code GE)
	<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners
	<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required (FULL assessment) in writing only via post/HPOS upload <del>Authority Required (in writing only via post/HPOS upload)</del>
	<b>Administrative advice:</b> No increase in the maximum number of repeats may be authorised.
	<b>Administrative advice:</b> Special Pricing Arrangements apply.
	<b>Indication:</b> Chronic treatment of hereditary angioedema Types 1 or 2
	<b>Treatment Phase:</b> Initial 3: New patient (transitioning from PBS-subsidised garadacimab)
	<b>Clinical criteria:</b>

	Patient must have been receiving garadacimab through the PBS as routine prophylaxis for hereditary angioedema immediately prior to receiving this drug.
	AND
	<b>Clinical criteria:</b>
	The treatment must not be used in combination with a C1-esterase inhibitor concentrate
	AND
	<b>Treatment criteria:</b>
	Must be treated by a clinical immunologist or a specialist allergist
	<b>Administrative advice:</b> <i>Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).  Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at <a href="http://www.servicesaustralia.gov.au">www.servicesaustralia.gov.au</a>  Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at <a href="http://www.servicesaustralia.gov.au/hpos">www.servicesaustralia.gov.au/hpos</a>  Or mailed to:  Services Australia  Complex Drugs  Reply Paid 9826  HOBART TAS 7001</i>

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

## 9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

## 10 Sponsor's Comment

CSL Behring welcomes the PBAC's decision to recommend the PBS listing of Andembry® and looks forward to working with the Department to make this treatment accessible to patients as soon as possible.