5.06 DONIDALORSEN, Solution for injection 80 mg in 0.8 mL pre-filled pen, Zirdawny®, Otsuka Australia Pharmaceutical Pty. Ltd.

1 Purpose of submission

1.1 The Category 2 submission requested a General Schedule Authority Required (Written) listing for donidalorsen (DONI) for the long-term prophylaxis (prevention) of recurrent attacks in patients with hereditary angioedema (HAE).

1.2 Listing was requested on the basis of a cost-minimisation approach (CMA) versus lanadelumab (LANA) as long-term prophylaxis (LTP) to prevent HAE attacks in the PBS target population. The submission also included garadacimab (GARA) as a relevant comparator.

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

Component	Description
Population	Hereditary angioedema (HAE)
Intervention	Donidalorsen
Comparator	Lanadelumab (and garadacimab[a])
Outcomes	• Time-standardised rate of HAE attacks from Week 1 to Week 25 • Time-standardised rate of HAE attacks from Week 5 to Week 25 • Time-standardised rate of moderate or severe HAE attacks • Clinical response (defined as a ≥50%, ≥70%, or ≥90% reduction in the attack rate from baseline) • Time-standardised rate of HAE attacks requiring on-demand therapy • Attack-free status • Change from baseline to Week 25 in the total score on the Angioedema Quality of Life (AE-QoL) Questionnaire • Safety
Clinical claim	Donidalorsen is non-inferior to lanadelumab with respect to efficacy and non-inferior with respect to safety. Donidalorsen is non-inferior to garadacimab with respect to efficacy and non-inferior with respect to safety.

[a] Garadacimab received a positive recommendation in November 2024, and was listed on the PBS on 1st April 2026.
Source: Table 7, p2 of the submission

2 Background

Registration status

2.1 The submission was made under the TGA/PBAC Parallel Process. Donidalorsen was registered by the TGA in June 2026 for the "routine prevention of recurrent attacks of hereditary angioedema (HAE) in adults and adolescents aged 12 years and older."

Previous PBAC consideration

2.2 This is first submission for DONI considered by the PBAC.

2.3 The current PBS listing for LANA (300 mg/2 mL subcutaneous [SC] injection presentation) is for the preventive treatment of HAE Type 1 or 2 attacks in patients aged ≥12 years. A submission requesting the listing of a new form of LANA (150 mg/1 mL injection) as a LTP for HAE in patients aged 2 to 11 years was considered at the November 2024 meeting. The PBAC recommended an age-agnostic listing for LANA for both formulations (paragraphs 7.1 and 7.3, LANA Public Summary Document [PSD], November 2024 PBAC meeting); however, the lower dose and age-agnostic change had not progressed to listing at the time of PBAC consideration.

2.4 Another LTP for HAE, GARA, received a positive recommendation at the November 2024 PBAC meeting on a cost-minimisation basis versus LANA (paragraph 7.1, GARA PSD, November 2024 PBAC meeting). It was listed on the PBS on 1 April 2026.

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

3 Requested listing

MEDICINAL PRODUCT medicinal product pack	Dispensed Price for Max. Qty	Max. qty packs	Max. qty units	№.of Rpts	Available brands
Donidalorsen solution for injection 80 mg in 0.8 mL pre-filled pen, 1	Published: $18,603.03[a] or $29,667.09[b] Effective: To be determined	1	1	5	Zirdawny Otsuka Australia Pharmaceutical Pty Ltd

[a] Based on the pricing proposal for donidalorsen for Approaches 1 and 2. See the "Economic analysis" section below for full details.
[b] Based on the pricing proposal for donidalorsen for Approach 3. See the "Economic analysis" section below for full details.

Requested restriction (Initial 1 – New patients commencing with no previous treatment with C1-INH or lanadelumab for routine prophylaxis)

Category / Program: GENERAL - General Schedule (Code GE)
Prescriber type: ☒Medical Practitioners
Restriction type: ☒Authority Required (in writing only via post/HPOS upload)
Condition: Hereditary angioedema Type 1 or 2
Indication: Chronic treatment of hereditary angioedema Types I and II
Treatment Phase: Initial 1: New patient (commencing with no previous treatment with C1-INH or lanadelumab for routine prophylaxis)
Clinical criteria:
Patient must have experienced at least 6 treated acute attacks of hereditary angioedema within the 3-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
Treatment Criteria:
Must be treated by a clinical immunologist or a specialist allergist
Prescribing Instructions: For the purposes of administering this restriction, acute attacks of hereditary angioedema are those of a severity necessitating immediate medical intervention with either (i) icatibant, or (ii) C1-esterase inhibitor concentrate The baseline measurement of the number of treated acute attacks of hereditary angioedema within the 3 months prior to initiating treatment must be provided at the time of submitting this application

Requested restriction (Initial 2 – New patients commencing from National Blood Authority-funded C1-INH)

Category / Program: GENERAL - General Schedule (Code GE)
Prescriber type: ☒Medical Practitioners
Restriction type: ☒Authority Required (in writing only via post/HPOS upload)
Condition: Hereditary angioedema Type 1 or 2
Indication: Chronic treatment of hereditary angioedema Types I and II
Treatment Phase: : Initial 2: New patient (commencing from National Blood Authority-funded C1-INH)
Clinical criteria:
Patient must have been receiving a C1-esterase inhibitor through the National Blood Authority as routine prophylaxis for hereditary angioedema immediately prior to receiving donidalorsen
AND
The treatment must not be used in combination with a C1-esterase inhibitor concentrate or lanadelumab
Treatment Criteria:
Must be treated by a clinical immunologist or a specialist allergist

Requested restriction (Initial 3 – New patients transitioning from PBS-subsidised LTP)

Category / Program: ☒GENERAL - General Schedule (Code GE)
Prescriber type: ☒Medical Practitioners
Restriction type: ☒Authority Required (in writing only via post/HPOS upload)
Condition: Hereditary angioedema Type 1 or 2
Indication: Chronic treatment of hereditary angioedema Types I and II
Treatment Phase: Initial 3: New patient (transitioning from PBS-subsidised LTP)
Clinical criteria:
Patient must have been receiving routine long-term prophylaxis through the PBS for hereditary angioedema immediately prior to receiving donidalorsen
AND
The treatment must not be used in combination with a C1-esterase inhibitor concentrate or lanadelumab
Treatment Criteria:
Must be treated by a clinical immunologist or a specialist allergist

LTP = long-term prophylaxis

Requested restriction (Continuing treatment)

Category / Program: ☒GENERAL - General Schedule (Code GE)
Prescriber type: ☒Medical Practitioners
Restriction type: ☒Authority Required (in writing only via post/HPOS upload)
Condition: Hereditary angioedema Type 1 or 2
Indication: Chronic treatment of hereditary angioedema Types I and II
Treatment Phase: Continuing preventative treatment
Clinical criteria:
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
Treatment Criteria:
Must be treated by a specialist allergist or clinical immunologist, or in consultation with a specialist allergist or clinical immunologist
Prescribing Instructions: Patients who have successfully transitioned to a lower dosing frequency should be reviewed every 6 months to ensure they continue to demonstrate a sustained response 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

3.1 The proposed published prices for DONI were based on the published LANA price. The submission did not propose an effective price for DONI as the sponsor was not aware of the effective prices of LANA or GARA.

3.2 The submission proposed the PBS listing of DONI for patients with HAE Types 1 and 2. The requested initiation restrictions were intended to include the following patient groups: (1) new patients commencing DONI with no previous treatment with C1 inhibitor (C1-INH) or LANA as LTP, (2) patients commencing from PBS-funded LTP, and (3) new patients commencing from National Blood Authority (NBA)-funded C1-INH. The evaluation noted the submission's proposed initiating restrictions would require minor revisions to reflect the recent PBS-listing of GARA as LTP.

3.3 The requested PBS listing was within the proposed TGA indication, except for the age criterion (age-agnostic in the PBS listing versus ≥ 12 years of age in the TGA indication). The requested age-agnostic PBS restriction for DONI was in line with previous PBAC decisions.

3.4 The proposed PBS restriction for DONI broadly aligned with the current restriction for the main comparator, LANA, with three proposed modifications:

- Shortening the time frame of eligibility assessment in terms of the HAE attack frequency, while maintaining the mean monthly attack requirement (i.e. changing from 12 attacks over 6 months to 6 attacks over 3 months), see paragraph 3.5.
- Introduction of a new restriction to allow switching from another LTP. A similar provision is included in the GARA listing.
- Removal of the age limit. An age-agnostic listing was recommended by the PBAC for both LANA and GARA, when their submissions were considered at the November 2024 meeting (paragraph 7.3, LANA PSD, November 2024 PBAC meeting; paragraph 7.12, GARA PSD, November 2024 PBAC meeting).

3.5 The requested initial treatment restriction included an eligibility criterion of at least 6 treated acute HAE attacks within the preceding 3-month period, which differed from the requirement in the existing LANA and for GARA restrictions of at least 12 treated acute HAE attacks within the preceding 6-month period. The submission argued that this change was to reduce unnecessary delays in access to effective prophylaxis, while targeting patients with active and clinically significant disease. Also, the submission noted that the shorter assessment time frame would be more consistent with the run-in periods in the clinical trials for LANA, GARA and DONI (1 – 2 months). The evaluation and the ESC considered that, given the variable nature of HAE attacks, the same mean number of HAE attacks per month does not guarantee comparable baseline risk if the assessment period differs. Although shortening the duration over which HAE attacks are measured may speed up access to patients who require LTP, it may also reduce the risk profile of patients accessing LTP because HAE attacks may be grouped around trigger events or may be associated with meteorological changes. Consequently, a proportion of patients who experience the requisite 6 attacks over 3 months may not meet the stricter eligibility criteria of 12 attacks over 6 months. Additionally, in its July 2021 consideration of lanadelumab for HAE, the PBAC considered the number of baseline HAE attacks (12 attacks in 6 months) was reasonable for eligibility. The PBAC's previous considerations had discussed the importance of ensuring use was targeted to a sufficiently high-risk population given the high cost of the drug per patient, and noting the ICER was highly sensitive to the baseline HAE attack rate (paragraphs 7.3 and 7.11, lanadelumab PSD, July 2020 PBAC meeting). The Pre-Sub-Committee Response (PSCR) stated that the proposed change would support more timely access and meaningful benefits for patients and their carers, without materially changing the patient population. The PSCR also stated that it considered that the revision would be equally appropriate for the current LANA and GARA restrictions, i.e. it was not proposed as a point of difference versus the existing therapies. The ESC noted that under the current LANA and GARA restrictions, patients with more severe disease and more frequent attacks can become eligible for treatment sooner than 6 months. Overall, the ESC considered the current eligibility timeframe likely remains fit for purpose.

3.6 The PSCR noted that the proposed TGA indication for DONI included HAE Type 3. The PSCR acknowledged that although direct clinical evidence in this subpopulation was limited, available Phase 2 evidence for 3 patients was presented in the submission. The PSCR noted this was a very small group of patients (the submission stated that there is 1 reported case in Australia) but stated there is an unmet need for these patients. However, the ESC considered that HAE Type 3 represents a different underlying disease mechanism compared with Types 1 and 2 and is heterogenous with less clearly defined diagnostic criteria. The ESC considered there was very limited clinical evidence in this group and no evidence to suggest that the economic evaluation for HAE Types 1 and 2 should apply to Type 3, noting also that C1-INH is only available on the NBA for HAE Types 1 and 2.

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

4 Population and disease

4.1 HAE is a rare, chronic, debilitating genetic disorder characterised by recurrent, unpredictable and potentially life-threatening swelling episodes in subcutaneous and submucosal tissues around the body that most commonly affect the extremities, face, abdomen, genitals and larynx. HAE is categorised into three subtypes (Types 1, 2, and 3) based on C1-INH levels and functional activity. The most common forms, HAE with C1-INH deficiency (Type 1) and HAE with C1-INH dysfunction (Type 2), are most often caused by inherited mutations in the SERPING1 gene, which encodes the C1-INH protein[1]. The exact prevalence of HAE is unknown and varied from 1 per 10,000 to 1 per 150,000 persons across studies, with a number of publications suggesting that 1 per 50,000 is likely the closest estimate[2,3,4,5,6]. Of the diagnosed HAE cases, Type 1 HAE accounts for approximately 85%, Type 2 HAE accounts for approximately 15%[7].

4.2 HAE Type 3 (also referred to as nC1-INH-HAE) is extremely rare and is associated with normal levels and functional activity of C1-INH. It is caused by alternative pathogenic mechanisms and mutations in genes (compared with Types 1 and 2), with multiple different genes involved.

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[1] Sinnathamby ES, Issa PP, *et al*. Hereditary Angioedema: Diagnosis, Clinical Implications, and Pathophysiology. *AdvTher*. 2023;40(3):814-27.

[2] Anderson J, Soteres D, *et al*. Physician- and patient-reported outcomes by hereditary angioedema type: Data from a real-world study. *Allergy Asthma Proc*. 2024;45(4):247-54.

[3] Bygum A. Hereditary angio-oedema in Denmark: a nationwide survey. *Br J Dermatol*. 2009;161(5):1153-8.

[4] Zanichelli A, Arcoleo F, *et al*. A nationwide survey of hereditary angioedema due to C1 inhibitor deficiency in Italy. *Orphanet J Rare Dis*. 2015;10:11.

[5] Lumry WR, Settipane RA. Hereditary angioedema: Epidemiology and burden of disease. *Allergy Asthma Proc*. 2020;41(Suppl 1):S08-s13.

[6] Aygören-Pürsün E, Magerl M, *et al*. Epidemiology of Bradykinin-mediated angioedema: a systematic investigation of epidemiological studies. *Orphanet J Rare Dis*. 2018;13(1):73.

[7] Bernstein JA. Severity of hereditary angioedema, prevalence, and diagnostic considerations. *Am J Manag Care*. 2018;24(14 Suppl):S292-s8.

4.3 HAE symptoms typically begin in childhood or early adulthood. The mean age of onset ranges from approximately 4.5 years to 11 years[3,8,9], with most cases presenting before 20 years of age[10]. An earlier onset of symptoms is associated with a more severe disease course[8,9]. Abdominal attacks and peripheral (cutaneous) attacks are the most common HAE attacks. While not typically life-threatening, these attacks can be painful, disfiguring, and significantly impair daily functioning and quality of life (QoL). Laryngeal attacks represent the most severe manifestation of HAE due to the risk of asphyxiation, permanent neurological injury, or death.

4.4 Patients with frequent, severe, or otherwise burdensome attacks are considered for LTP. In current Australian clinical practice, LANA is the most commonly used LTP medicine. It is subsidised through the PBS for patients with HAE Types 1 and 2 who have experienced at least 12 treated attacks in a 6-month period before commencing LANA. C1-INH for LTP is funded through the NBA as intravenous (IV) or SC formulations. IV or SC C1-INH is typically reserved for patients with very high attack burden (typically at least 8 attacks per month), for those requiring stringent disease control, or for patients for whom LANA is unsuitable. GARA was added to the PBS during the evaluation, with the same indication as LANA.

4.5 DONI was proposed as an alternative LTP option alongside LANA, GARA and C1-INH. DONI was proposed for the treatment of HAE Types 1 and 2 in patients who have experienced at least 6 treated attacks in a 3-month period before commencing DONI. The submission proposed that patients receiving LANA, GARA or C1-INH would be able to switch to DONI.

4.6 DONI is a first-in-class, ribonucleic acid (RNA)-targeted antisense oligonucleotide that binds to prekallikrein messenger ribonucleic acid (mRNA) in the liver, thereby promoting the degradation of prekallikrein-encoding mRNA and decreasing plasma prekallikrein protein levels. This directly impacts the plasma kallikrein-kinin system and subsequent release of bradykinin, including in patients with HAE with normal C1-INH. It is the release of bradykinin which causes vasodilation and increased permeability, leading to angioedema[11,12]. DONI offers a distinct mechanism of action, compared with LANA (acting on circulating components of the kallikrein-kinin pathway) and GARA (inhibiting activated factor XII and thereby blocking the kallikrein-kinin pathway). The submission noted that the RNA-mediated mechanism of DONI and

[8] Bork K, Meng G, *et al*. Hereditary angioedema: new findings concerning symptoms, affected organs, and course. *Am J Med*. 2006;119(3):267-74.

[9] Farkas H. Pediatric hereditary angioedema due to C1-inhibitor deficiency. *Allergy Asthma Clin Immunol*. 2010;6(1):18.

[10] Henao MP, Kraschnewski JL, *et al*. Diagnosis and screening of patients with hereditary angioedema in primary care. *Ther Clin Risk Manag*. 2016;12:701-11.

[11] Kaplan AP, Joseph K. Pathogenic mechanisms of bradykinin mediated diseases: dysregulation of an innate inflammatory pathway. *Adv Immunol*. 2014;121:41-89.

[12] Riedl MA, Tachdjian R, *et al*. Efficacy and Safety of Donidalorsen for Hereditary Angioedema. *N Engl J Med*. 2024;391(1):21-31.

its relatively long half-life (approximately 30-31 days versus 14 days for LANA and 18 days for GARA) enable gradual suppression of prekallikrein levels rather than rapid transient functional inhibition of circulating prekallikrein in the bloodstream.

4.7 The recommended starting dose of DONI is 80 mg via subcutaneous (SC) injection. Doses should be administered once monthly. The Product Information (PI) states that a dosing interval of 80 mg once every 2 months may be considered if the patient is well controlled (e.g., attack free) for at least 3 months while receiving DONI.

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

5 Comparator

5.1 The submission nominated LANA as the main comparator. The key argument provided in support of this nomination was that LANA was the only LTP for HAE available on the PBS when the submission was prepared (GARA was listed on the PBS on 1 April 2026). The ESC considered that LANA was the appropriate main comparator.

5.2 The submission also included GARA as a relevant comparator. The ESC considered that this was also reasonable.

5.3 Of note, LANA was recommended for listing based on acceptable cost-effectiveness assuming LANA 300 mg every 4 weeks (Q4W) dosing, with a RSA to mitigate the risk of expenditure exceeding the estimated financial impact based on Q4W dosing, i.e. more frequent Q2W dosing of LANA (paragraphs 7.5 and 7.7, LANA PSD, July 2021 PBAC meeting). When the GARA submission was reviewed, the ESC considered that, although in practice LANA appears to be used more frequently by a substantial proportion of patients, the CMA should compare GARA to LANA Q4W, as this reflects the basis upon which the PBAC recommended that LANA would be cost-effective (paragraph 6.44, GARA PSD, November 2024 PBAC meeting). The equi-effective dose of LANA accepted by the PBAC (i.e. LANA 7,821 mg over 2 years[13], paragraph 7.7, GARA PSD, November 2024 PBAC meeting) was based on the LANA Q4W regimen.

5.4 In the context of the cost-minimisation approach taken by the submission, a further consideration for PBAC is that, under Section 101(3B) of the *National Health Act 1953*, when the proposed medicine is substantially more costly than an alternative therapy, the committee cannot make a positive recommendation unless it is satisfied that, for some patients, the proposed medicine provides a significant improvement in efficacy and/or reduction of toxicity over the alternative therapy. If the committee is so satisfied, it must make a statement to this effect.

5.5 For the requested population, GARA may be considered as an alternative therapy because it could be replaced in practice.

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

[13] 7,821 mg = 300 mg Q4W x 26.1 doses, where 26.1 was calculated as 365.25x2/(4x7).

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer inputs

6.2 The PBAC noted and welcomed the input from individuals (30), a health care professional (1) and organisations (2) via the Office of Health Technology Assessment Consultation Hub. The inputs from individuals described the severe and unpredictable nature of the condition, which involves painful attacks that can be difficult to control and have a major impact on mental health.

6.3 The comments described the advantages of having another option available for patients with HAE, particularly given donidalorsen has a different mechanism of action compared with other available therapies, which would allow for individualised therapy as not all patients respond the same way to different therapies. The Australasian Society of Clinical Immunology and Allergy (ASCIA) stated "different medications for HAE LTP have different mechanisms or action and/or routes of administration, and providing a range of LTP options enables patients and their treating specialist to select the most suitable treatment for their individual circumstances."

6.4 Donidalorsen was also described as being easier to administer than other therapies due to the pre-filled pen device. The reduced administration frequency of donidalorsen (Q4W or Q8W) was also viewed favourably.

6.5 The comments acknowledged uncertainties regarding the long-term safety of donidalorsen but considered this was acceptable given the severity and burden of HAE. It was noted that older therapies, such as danazol, are associated with significant long-term adverse effects. Consumers highlighted that donidalorsen offers a different safety profile, which may be preferred by some patients.

Clinical trials

6.6 No head-to-head trials were identified that directly compared DONI and LANA or DONI and GARA as LTP in the proposed PBS target population. Thus, the submission presented anchored ITCs using the Bucher method, via placebo (PBO) as the common reference:

- For the ITC between DONI and LANA, the trials used were one Phase III randomised controlled trial (RCT) which compared DONI (Q4W and Q8W) with PBO (OASIS-HAE), and one Phase III RCT which compared LANA (Q2W and Q4W) with PBO (HELP).
- For the ITC between DONI and GARA, the trials used were the OASIS-HAE trial and one Phase III RCT which compared GARA (Q4W) with PBO (VANGUARD).

6.7 Details of the trials presented in the submission are provided in Table 2.

Table 2: Trials and associated reports presented in the submission – indirect comparison

Trial ID	Protocol title/ Publication title	Publication citation
Donidalorsen vs. placebo		
OASIS-HAE NCT05139810	Clinical study report: OASIS-HAE. A Phase 3 Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of ISIS 721744 in Patients with Hereditary Angioedema (HAE)	July 2024
	Riedl MA, Tachdjian R, et al. Efficacy and Safety of Donidalorsen for Hereditary Angioedema.	*NEJM* 2024, 391(1): 21-31.
	Riedl MA, Yarlas A, et al. Patient-Reported Outcomes in the Phase III OASIS-HAE Study of Donidalorsen for Hereditary Angioedema. Allergy:	*European Journal of Allergy and Clinical Immunology* 2025, 80(8): 2361-2368.
	Longhurst HJ, Cancian M, et al. Hereditary Angioedema Attacks in Patients Receiving Long-Term Prophylaxis: A Systematic Review.	*Clinical Reviews in Allergy and Immunology* 2024, 67(1): 83-95.
	Raja A, Shuja MH, et al. Efficacy and safety of Donidalorsen in Hereditary Angioedema with C1 inhibitor deficiency: a systematic review and a meta-analysis.	*Archives of Dermatological Research* 2025, 317(1).
OASISplus (Open label extension of OASIS)	Lumry WR, Tachdjian R, et al. Donidalorsen for Long-Term Prophylaxis of Hereditary Angioedema Attacks: Results from the OASISplus Open-Label Extension Cohort at Year 1.	*Journal of Asthma and Allergy*, 2026, 592079.
	Riedl MA, Bernstein JA, et al. Donidalorsen treatment of hereditary angioedema in patients previously on long-term prophylaxis.	*The Journal of Allergy and Clinical Immunology: In Practice*, 2025
Lanadelumab vs. placebo		
HELP NCT02741596	Banerji A, Riedl MA, et al. Effect of lanadelumab compared with placebo on prevention of hereditary angioedema attacks: a randomized clinical trial.	*JAMA* 2018; 320(20): 2108-2121
	Lumry WR, Weller K, et al. Impact of lanadelumab on health-related quality of life in patients with hereditary angioedema in the HELP study.	*Allergy: European Journal of Allergy and Clinical Immunology* 2021, 76(4): 1188-1198.
	Riedl MA, Maurer M, et al. Lanadelumab demonstrates rapid and sustained prevention of hereditary angioedema attacks	*Allergy*. 2020;75(11):2879-2887
Garadacimab vs. placebo		
VANGUARD CSL312-3001 NCT04656418	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.	*Lancet* 2023; 401(10382):1079-1090 Journal of Allergy and Clinical Immunology 2023; 151:2 Suppl (AB132)

Source: Table 18, pp35-40 of the submission
Notes: Blue shading indicates the trials/publications previously considered by the PBAC.
Clinical trial registry records were not included in the table.

6.8 In OASIS-HAE, a total of 91 patients aged ≥12 years, with HAE Types 1 or 2, were randomised during an up to 8-week screening period after experiencing ≥2 HAE attacks. Randomisation was conducted in a 2:1 ratio to the Q4W cohort (Cohort A) or Q8W cohort (Cohort B), with patients within each cohort further randomised to DONI or matched PBO; PBO patients from both cohorts were pooled for analysis. There were imbalances between treatment arms for some baseline characteristics that were likely due to the small patient numbers (n = 23 for the DONI 80 mg Q8W arm and n = 22 for the pooled PBO arm). Imbalances included: i) the number of HAE attacks over the prior

12-month period (mean: 29.1 attacks in PBO vs. 45.7 attacks and 33.3 attacks in the DONI Q4W and DONI Q8W arms, respectively), and ii) the mean HAE attack rate per 4 weeks during the Run-in period (2.90 for PBO versus 3.61 for DONI Q4W, and 3.18 for DONI Q8W). Notably, the mean attack rate was lower for PBO compared with those observed in the two DONI regimen arms. Recognising the small patient numbers and the potential for random variation, patients who were randomly assigned to the PBO arms may have had less severe disease than those assigned to the DONI arms.

6.9 The primary endpoint in the key trial OASIS-HAE was the time-normalised number of investigator-confirmed HAE attacks from Week 1 to Week 25 for DONI Q4W, with the number of HAE attacks for DONI Q8W as a secondary outcome. The DONI Q8W arm in OASIS-HAE was a treatment initiating arm (not a down titration arm in patients who were well controlled, as per the proposed product information) and therefore may have limited relevance to the current evaluation.

6.10 Given the mechanism of action of DONI (see paragraph 4.6), there is a delayed onset of maximum treatment effect for about 4-5 weeks after initiation[14]. Thus, most secondary endpoints for DONI were analysed (per protocol and in the submission) for the period from Week 5 to Week 25. The submission stated this analysis window was pre-specified in the OASIS-HAE protocol to "capture treatment effects after the anticipated establishment of DONI's pharmacodynamic activity". The ESC and the PBAC considered that the clinical relevance of the delayed onset was limited given that treatment in OASIS-HAE was until Week 25, and in clinical practice, therapy is likely to be ongoing.

6.11 Each of the individual clinical trials included in the ITCs had a double-blinded study design with a low risk of bias. However, the evaluation considered that the risk of bias associated with the ITCs was high. Transitivity issues among the OASIS-HAE, HELP, and VAGUARD trials include:

- Trial conduct period: the OASIS-HAE and VANGUARD trials were conducted 4-5 years later than the HELP trial (2021-2023 vs. 2016-2017). It is possible that more preventive treatment options were available in OASIS-HAE and VANGUARD.
- Washout period: the OASIS-HAE trial applied a half-life-based wash out period (duration ranging from 2 to 10 weeks dependent on the type of prior prophylactic therapy), whereas HELP and VANGUARD applied fixed wash out durations of 4 weeks and 2 weeks, respectively.

[14] DONI targets prekallikrein mRNA in hepatocytes and existing plasma prekallikrein must degrade before the onset of the clinical effect. As the estimated plasma half-life of prekallikrein is approximately 5 days, the efficacy of the product would be expected towards the end of the first 4-week dosing period (p177, European Medicines Agency [EMA]; Committee for Medicinal Products for Human Use [CHMP] Assessment Report EMA/CHMP/303940/2025).

- HAE attack definition: in the HELP trial, HAE attacks that lasted ≤8 hours were not counted as attacks, the definition of HAE attacks in the other two trials did not limit to the duration of attacks.
- Run-in attack rate: in OASIS-HAE, the mean baseline attack rate per month was 3.6 in the DONI Q4W arm and 2.9 in the PBO arm. This was higher than that in the VANGUARD trial (3.1 in the GARA arm and 2.5 in the PBO arm) and lower than that in the HELP trial (3.7 in the LANA 300 mg Q4W arm and 4.0 in the PBO arm).
- History of prophylactic therapy: the percentages of patients receiving prior prophylactic therapy in OASIS-HAE, HELP, and VANGUARD trials were 17.8%, 56.0%, 32.8%, respectively. Recognising the small size of trial populations, this difference suggested that the patients in HELP had more severe disease compared to those in the OASIS-HAE and VANGUARD trials.

6.12 The key features of the randomised trials included in the ITCs are summarised in Table 3.

Table 3: Key features of the included evidence – indirect comparison

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
Donidalorsen vs. placebo						
OASIS-HAE	91	R, DB 24 wks	Low[a]	HAE Types I and II patients aged ≥ 12 years with ≥ 2 HAE attacks during the 8-week screening period	• Time-normalised number of HAE attacks from Week 1 to Week 25 • Time-normalised number of HAE attacks from Week 5 to Week 25 • Number of patients with a clinical response[b] in HAE attack rate between Week 5 to Week 25 • Proportion of HAE attack-free patients from Week 5 to Week 25 • Time normalised number of moderate or severe HAE attacks from Week 5 to Week 25 • Time normalised number of HAE attacks requiring acute HAE therapy from Week 5 to Week 25 • Change in Angioedema-QoL questionnaire total score at Week 25 • Safety	No
Lanadelumab vs. placebo						
HELP	125[c]	R, DB 26 wks	Low[a]	HAE Types I and II patients aged ≥ 12 years with ≥ 3 HAE attacks during the 3 months before screening	• Time-normalised number of HAE attacks from Day 1 to Day 182 • Proportion of HAE attack-free patients • Time normalised number of moderate or severe HAE attacks • Time-normalised number of HAE attacks requiring acute therapy • Change from baseline in Angioedema-QoL total score • Safety	No
Garadacimab vs. placebo						
VANGUARD	64	R, DB 26 wks	Low[a]	HAE Types I and II patients aged ≥ 12 years with ≥ 1 HAE attack per month	As above	No

Source: Complied 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; QoL = quality of life; R = randomised; wks = weeks
[a] 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.
[b] Defined as a ≥50%, ≥70% or ≥90% reduction from baseline in investigator-confirmed HAE attack rate
[c] 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 trials previously considered by PBAC

6.13 The submission also presented data from an open-label extension (OLE) study (OASISplus; N = 147) as supplementary evidence. The OLE study consisted of two cohorts:

- Rollover cohort (n=83): Patients who completed the double-blind treatment period in OASIS-HAE were eligible to continue into the OLE study, where they received DONI for up to an additional 104 weeks.
- Switch cohort (n=64): This cohort consisted of patients who were previously maintained on other HAE prophylactic medications (LANA, C1-INH or berotralstat[15]) for at least 12 weeks prior to the OASISplus Run-in period.

6.14 OASISplus was non-comparative and not included in the ITCs. The primary outcome in OASISplus was the incidence and severity of treatment-emergent adverse events (TEAEs). This OLE study also reported efficacy outcomes, such as time-normalised number HAE attacks.

Comparative effectiveness

DONI versus PBO

6.15 The results of the time-normalised investigator-confirmed HAE attack rate (per 4 weeks) from Week 1 to Week 25 for DONI Q4W (primary endpoint) and for DONI Q8W (secondary outcome), compared with PBO, are presented in Table 4.

Table 4: HAE attack rate from Week 1 to Week 25 – OASIS-HAE

Time-normalised HAE attacks	DONI 80 mg Q4W (N = 45) Primary analysis	DONI 80 mg Q8W (N = 23) Secondary analysis	PBO (N=22)
Run-in period HAE attack rate (per 4 weeks) [a]			
Mean (SD, SEM)	3.61 (2.24, 0.33)	3.18 (2.15, 0.45)	2.90 (1.66, 0.35)
Time-normalised HAE attack rate (per 4 weeks) from Week 1 to Week 25[b]			
Mean (SD, SEM)	0.89 (1.85, 0.28)	1.19 (1.63, 0.34)	2.29 (1.81, 0.39)
Poisson regression[c]			
Least square mean rate (95% CI)	0.44 (0.27, 0.73)	1.02 (0.65, 1.59)	2.26 (1.66, 3.09)
Model adjusted mean rate ratio (95% CI)	0.19 (0.11, 0.35)	0.45 (0.26, 0.78)	
Wald Chi-square p-value	**p<0.001**	**p=0.004**	
Mean difference versus PBO (95% CI)	**-1.82 [-2.65, -0.99] [e]**	**-1.24 [-2.19, -0.29] [e]**	
Percentage difference versus PBO (95% CI)[d]	**-81% (-89.3%, -64.9%)**	**-55% (-73.9%, -22.3%)**	

Source: Table 29, p85 of the submission.

CI = confidence interval; DONI = donidalorsen; HAE = hereditary angioedema; PBO = placebo; Q4W/Q8W = every 4 weeks/every 8 weeks; SD = standard deviation; SEM = standard error of mean.

Bolded = Statistically significant.

[a]The run-in period (Screening) HAE attack rate (per month) for each patient was calculated as the number of investigator-confirmed HAE attacks that occurred during the run-in period divided by the number of days the patient contributed to the run-in period and then multiplied by 28.

[b]The time-normalised HAE attack rate (per month) was calculated as the number of investigator-confirmed HAE attacks that occurred from Week 1 to Week 25, divided by the number of days the patient contributed to that period, and then multiplied by 28.

[c]The Poisson regression model included treatment groups, baseline (the run-in period HAE attack rate), the treatment-by-baseline interaction as a covariate, and the logarithm of time per month that each patient was observed from Week 1 to Week 25 used as an offset variable

[15] As of April 2026, berotralstat is not registered in Australia for routine prevention of HAE.

(e.g., log (6) if the patient stayed in the study for 24 weeks). Pearson chi-square scaling of standard errors was used to account for potential overdispersion.

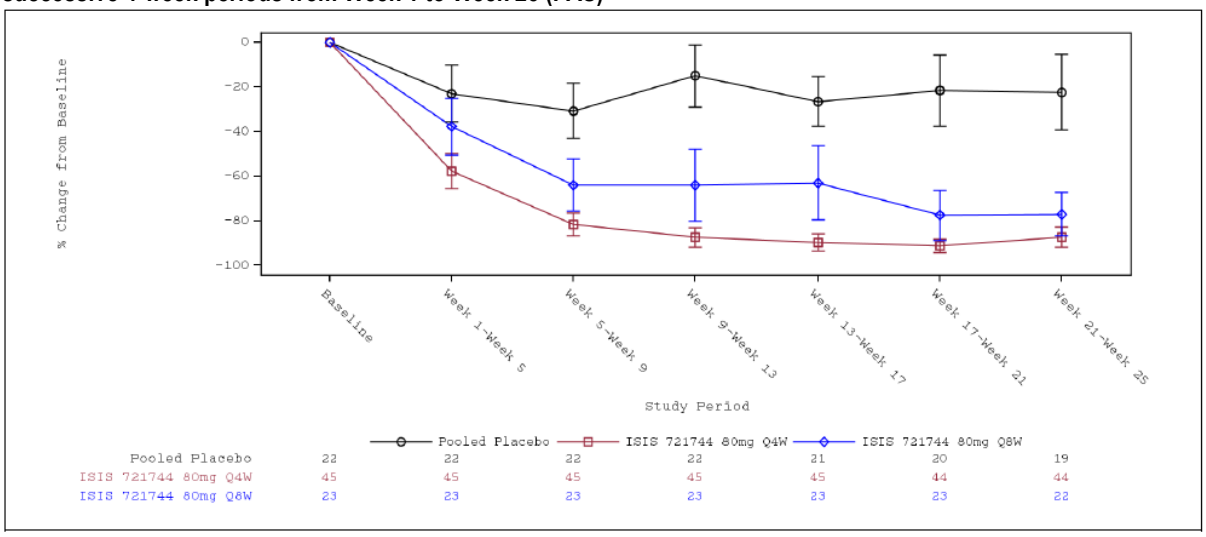
[d]The percentage difference in mean investigator-confirmed HAE attack rate between donidalorsen and PBO groups were calculated as 100% * (mean rate ratio -1). Similarly, the estimated upper and lower confidence limits for the mean rate ratio can be transformed by subtracting 1 and multiplying by 100% to calculate 95% CI for the percentage change.

[e]Estimated from least square mean (95%CI) using Review Manager version 5.4.1

6.16 The least squares mean (LSM) time-normalised investigator-confirmed HAE attack rate (per 4 weeks) from Week 1 to Week 25 was 0.44 (95% confidence interval [CI]: 0.27, 0.73) for the DONI 80 mg Q4W arm and 2.26 (95% CI: 1.66, 3.09) for the PBO arm, representing a statistically significant 81% reduction (95% CI: -89.3%, -64.9%) relative to PBO for DONI Q4W (p<0.001). DONI 80 mg Q8W was associated with a 55% reduction (95% CI: -73.9%, -22.3%) in time-normalised attack rate from Week 1 to Week 25 relative to PBO. The Poisson regression model substantially reduced the mean attack rate in the DONI 80 mg Q4W arm (from a mean of 0.89 to a least square mean of 0.44) though the impact was far lesser in the other arms (e.g. in the placebo arm, the Poisson regression model only reduced the mean attack rate from 2.29 to a least square mean of 2.26). This was likely due to imbalances in covariates due to the small patient sample sizes.

6.17 Figure 1 shows the change in time-normalised, investigator-confirmed HAE attack rates (per 4 weeks) over time in the OASIS-HAE trial.

Figure 1: Percent change from baseline mean (± SEM) of investigator-confirmed HAE attack rate (Per 4 Weeks) over successive 4-week periods from Week 1 to Week 25 (FAS)



Source: Figure 2, p87 of the OASIS-HAE Clinical Study Report.

FAS = full analysis set; HAE = hereditary angioedema; ISIS 721744 = donidalorsen (DONI); Q4W = once every 4 weeks; Q8W = once every 8 weeks; SEM = standard error of mean

For Investigator-confirmed HAE attacks, the baseline rate, (i.e., Run-in Period Investigator-confirmed HAE attack rate), was calculated for each patient as the number of Investigator-confirmed HAE attacks that occurred during the Run-in Period divided by the number of days contributed to the Run-in Period multiplied by 28 days.

Note: The per 4-week HAE attack rate was calculated for each patient as number of HAE attacks occurring during each 4-week period divided by the number of days the patient contributed to the period multiplied by 28. Week 1 to Week 5 starts from Day 1 to Day 28; Week 5 to Week 9 starts from Day 29 to Day 56;Week 9 to Week 13 starts from Day 57 to Day 84; Week 13 to Week 17 starts from Day 85 to Day 112, and so on. Error bars indicate the standard error of the mean.

6.18 The DONI Q4W arm (red line) showed a larger reduction in attack rate compared to the PBO arm (black line) during Weeks 1 to 5. The reduction in attack rate in the DONI Q4W arm became larger from Week 5 to Week 9 which was sustained over the remainder of the treatment period, supporting the expected delayed onset of maximum treatment effect of DONI. For the DONI Q8W group (blue line), the reduction in HAE attacks progressively became larger over time and approached that of the DONI Q4W group by Week 25. The less frequent dosing regimen likely required a longer time for DONI to achieve steady state.

6.19 Results for time normalised HAE attack rate from Week 5 to Week 25 (secondary outcome) are summarised in Table 5.

Table 5: HAE attack rate from Week 5 to Week 25 – OASIS-HAE

Time-Normalised HAE Attacks	DONI 80 mg Q4W (N = 45)	DONI 80 mg Q8W (N = 23)	PBO (N=22)
Run-in period HAE attack rate (per 4 weeks) [a]			
Mean (SD, SEM)	3.61 (2.24, 0.33)	3.18 (2.15, 0.45)	2.90 (1.66, 0.35)
Time-normalised HAE attack rate (per 4 weeks) from Week 1 to Week 25[b]			
Mean (SD, SEM)	0.75 (1.90, 0.28)	1.09 (1.71, 0.36)	2.32 (1.93, 0.41)
Poisson regression[c]			
Least square mean rate (95% CI)	0.30 (0.15, 0.58)	0.90 (0.53, 1.52)	2.25 (1.59, 3.18)
Model adjusted mean rate ratio (95% CI)	0.13 (0.06, 0.28)	0.40 (0.21, 0.75)	
Wald Chi-square p-value	**p<0.001**	**p=0.004**	
Mean difference versus PBO (95% CI)	**-1.95 [-2.87, -1.03] [e] 0.0000**	**-1.35 [-2.42, -0.28] [e] p=0.0169**	
Percentage difference versus PBO (95% CI)[d]	**-87.0% (-93.8%, -71.9%)**	**-60.0% (-78.8%, -25.2%)**	

Source: Table 31, p89 of the submission.

CI = confidence interval; DONI = donidalorsen; HAE = hereditary angioedema; PBO = placebo; Q4W/Q8W = every 4 weeks/every 8 weeks; SD = standard deviation; SEM = standard error of mean.

Bolded = Statistically significant

[a]The run-in period (Screening) HAE attack rate for each patient was calculated as number of investigator-confirmed HAE attacks occurring during the run-in period divided by the number of days the patient contributed to the run-in period and then multiplied by 28.

[b]The time-normalised HAE attack rate was calculated as number of investigator-confirmed HAE attacks occurring from Week 5 to Week 25, divided by the number of days the patient contributed to the period multiplied by 28.

[c]The Poisson regression model included treatment groups, Baseline (the run-in period HAE attack rate), the treatment-by-baseline interaction as a covariate, and the logarithm of time in per month that each patient was observed from Week 5 to Week 25 used as an offset variable (e.g., log (6) if the patient stayed in the study for 24 weeks). Pearson chi-square scaling of standard errors was used to account for potential overdispersion.

[d]The percentage difference in mean investigator-confirmed HAE attack rate between DONI 80 mg and PBO groups were calculated as 100% × (mean rate ratio -1). Similarly, the estimated upper and lower confidence limits for the mean rate ratio were transformed by subtracting 1 and multiplying by 100% to calculate 95% CI for the percentage change.

[e]Estimated from least square mean (95% CI) using Review Manager version 5.4.1

6.20 The relative reduction of HAE attacks (from Week 5 to Week 25) in the DONI Q4W arm, as compared to placebo, was statistically significant and slightly higher (87.0%) than that reported for the whole treatment period from Week 1 to Week 25 (87% reduction vs. 81.0% reduction). These results should be interpreted with caution as a comparison between Week 1 to Week 25 and Week 5 to Week 25 are not mutually

exclusive. Given the small sample size of the patients, the results have limited precision as reflected by a large overlap between the 95% CIs.

6.21 Clinical response rate was analysed by the number of patients with a ≥ 50%, ≥ 70%, or ≥ 90% reduction from baseline in HAE attacks (per 4 weeks) from Week 5 to Week 25 in each treatment arm. Of these thresholds, only ≥ 70% was included in the efficacy hierarchical testing. The percentage of patients with a ≥ 70% reduction from baseline in investigator-confirmed HAE attacks from Week 5 to Week 25 was statistically greater in the DONI Q4W arm than in the PBO arm (82.2% vs. 18.2%; p<0.001). Of the 45 patients in the DONI Q4W arm, 24 (53.3%) patients were HAE attack-free from Week 5 to Week 25, compared with 2 of 22 (9.1%) patients in the PBO arm. This difference was statistically significant (p = 0.003).

6.22 Compared with PBO, DONI Q4W was associated with a lower time-normalised moderate or severe HAE attack rate (per 4 weeks; mean: 0.37 vs. 1.35) and a lower time-normalised HAE attack rate (per 4 week) requiring acute therapy from Week 5 to Week 25 (mean: 0.47 vs. 1.88).

6.23 The mean total score reduction (improvement) from baseline in the Angioedema-QoL total score at Week 25 was 24.7 points for the DONI Q4W arm, 21.3 points for the DONI Q8W arm, and 6.2 points for the PBO arm. The reductions in score from baseline at Week 25 versus PBO were considered clinically meaningful (i.e., ≥ 6 points)[16].

6.24 In the rollover cohort from the OLE study (OASISplus), the mean time-normalised HAE attack rate was 3.5 in the DONI Q4W arm at baseline, which decreased (improved) to 0.2 at Week 52, representing an approximately 94% reduction in HAE attack rate. A similar improvement was observed in the Q8W arm (from 2.9 at baseline to 0.1 at Week 52, approximately 95% reduction). Results demonstrated a sustained suppression of disease activity for DONI through 1 year. Patients switching from any prior LTP had a mean 62% reduction in HAE attacks from baseline (with the prior LTP) after receiving DONI Q4W for 16 weeks. After switching to DONI (presumably regardless of dosing regimen), mean HAE attack rate reductions from baseline were 65%, 41%, and 73% for patients switching from LANA, C1-INH, and berotralstat, respectively. Results from OASISplus (for both cohorts) should be interpreted with caution, due to the potential for selection bias (patients with a more favourable safety and efficacy profile tend to be enrolled in the OLE study) and the lack of a comparator arm.

ITCs: DONI versus LANA and DONI versus GARA

6.25 Results of the ITC for mean HAE attacks per month for the treatment period Week 1 to Week 25 (full treatment period) for DONI Q4W, and Week 0-Week 26 (full treatment period) for LANA and GARA are presented in Table 6. The DONI Q8W arm

[16] Weller, K., et al. (2016). "The Angioedema Quality of Life Questionnaire (AE-QoL)–assessment of sensitivity to change and minimal clinically important difference." Allergy 71(8): 1203-1209.

is not included as this dosing regimen was not recommended for initiating treatment in the PI.

Table 6: ITC of time-normalised HAE attacks per month: full treatment periods (Week 1 to Week 25 for DONI and Week 0 to Week 26) for active comparators

DONI arm (Week 1 to Week 25)	Active comparators (Week 0 to Week 26)	DONI vs PBO, mean difference [95% CI]	Active comparators vs PBO, mean difference [95% CI]	DONI vs active comparators, mean difference [95% CI]; (p-value)
DONI Q4W	LANA Q2W	-1.82 [-2.65, -0.99]	-1.71 [-2.13, -1.29]	-0.11 [-1.04, 0.82]; (0.8167)
	LANA Q4W		-1.44 [-1.88, -1.00]	-0.38 [-1.32, 0.56]; (0.4279)
	GARA Q4W		-1.85 [-2.65, -1.05]	0.03 [-1.12, 1.18]; (0.9593)

Source: Table 52, p116 of the submission.
CI = confidence interval; DONI = donidalorsen; GARA = garadacimab; HAE = hereditary angioedema; ITC = indirect treatment comparison; LANA = lanadelumab; MD = mean difference; Q2W = every 2 weeks; Q4W = every 4 weeks

6.26 The ITC results of the time-normalised numbers of HAE attacks per month numerically favoured DONI Q4W compared with LANA Q2W and LANA Q4W. There was no difference in the point estimates of the mean difference (MD) between DONI Q4W and GARA Q4W. The evaluation considered that the ITC results should be interpreted with caution as the 95% CIs are imprecise and wide.

6.27 Given there is a short time lag to the achievement of maximum therapeutic effects with DONI (reflecting DONI's mechanism of action), the submission presented an ITC of mean number of attacks using the Week 5 to Week 25 data in OASIS-HAE (i.e., after maximum efficacy of DONI was achieved) (Table 7).

Table 7: ITC of time-normalised HAE attacks per month: Week 5 to Week 25 for DONI and full treatment periods (Week 0 to Week 26) for active comparators

DONI arm (Week 5 to Week 25)	Active comparators (Week 0 to Week 26)	DONI vs PBO, mean difference [95% CI]	Active comparators vs PBO, mean difference [95% CI]	DONI vs active comparators, mean difference [95% CI]; (p-value)
DONI Q4W	LANA Q2W	-1.95 [-2.87, -1.03]	-1.71 [-2.13, -1.29]	-0.24 [-1.25, 0.77] (0.6418)
	LANA Q4W		-1.44 [-1.88, -1.00]	-0.51 [-1.53, 0.51] (0.3270)
	GARA Q4W		-1.85 [-2.65, -1.05]	-0.10 [-1.32, 1.12] (0.8723)

Source: Table 53, p116 of the submission.
CI = confidence interval; DONI = donidalorsen; GARA = garadacimab; HAE = hereditary angioedema; ITC = indirect treatment comparison; LANA = lanadelumab; MD = mean difference; Q2W = every 2 weeks; Q4W = every 4 weeks
Note: An indirect MD < 0 indicates a result favouring DONI

6.28 The ITC results of the number of time-normalised HAE attacks per month using the Week 5 to Week 25 treatment period for DONI Q4W numerically favoured DONI compared with full treatment period for LANA Q2W, LANA Q4W, and GARA Q4W. However, the 95% CIs are imprecise and wide. Using a treatment period of Week 5 to Week 25 for DONI Q4W will likely overestimate the comparative effectiveness as the HAE attack rate for DONI tends to be high during the first 4-5 weeks.

6.29 ITCs of the mean number of moderate to severe HAE attacks per month and the mean number of HAE attacks requiring on-demand medication per month (Week 5 to Week 25) compared with the full treatment period for the active comparators were consistent with the results of the primary ITC analysis. The point estimates generally favoured DONI Q4W.

6.30 Table 8 summarises the ITC of attack-free patients for DONI Q4W (Week 5 to Week 25) and for the active comparators (full treatment period).

Table 8: ITC of attack-free patients from Week 5 to Week 25 for DONI and full treatment periods for the active comparators

	Comparison	Intervention n/N (%)	PBO n/N (%)	OR (95% CI)	RD (95% CI) p-value
DONI Q4W (Week 5 to 25) versus LANA Q2W (Week 0 to Week 26)					
OASIS-HAE	DONI Q4W vs PBO	24/45 (53.3)	2/22 (9.1)	11.43 [2.38, 54.77]	0.44 [0.25, 0.63]
HELP	LANA Q2W vs PBO	9/27 (31.0)	1/41 (2.4)	20.00 [2.35, 169.91]	0.31 [0.12, 0.49]
Indirect comparison	DONI Q4W vs LANA Q2W			0.57 [0.04, 8.12]	0.13 [-0.14, 0.40] p=0.3366
DONI Q4W (Week 5 to 25) versus LANA Q4W (Week 0 to Week 26)					
OASIS-HAE	DONI Q4W vs PBO	24/45 (53.3)	2/22 (9.1)	11.43 [2.38, 54.77]	0.44 [0.25, 0.63]
HELP	LANA Q4W vs PBO	12/29 (44.4)	1/41 (2.4)	28.24 [3.40, 234.63]	0.39 [0.20, 0.57]
Indirect comparison	DONI Q4W vs LANA Q4W			0.40 [0.03, 5.64]	0.05 [-0.22, 0.32] p=0.7117
DONI Q4W (Week 5 to 25) versus GARA Q4W (Week 0 to Week 26)					
OASIS-HAE	DONI Q4W vs PBO	24/45 (53.3)	2/22 (9.1)	11.43 [2.38, 54.77]	0.44 [0.25, 0.63]
VANGUARD	GARA Q4W vs PBO	24/39 (62.0)	0	80.61 [4.57, 1422.09]	0.62 [0.46, 0.78]
Indirect comparison	DONI Q4W vs GARA Q4W			0.14 [0.01, 3.73]	-0.18 [-0.43, 0.07] p=0.1555

Source: Table 54, p119 of the submission

DONI = donidalorsen; LANA = lanadelumab; GARA = garadacimab; PBO = placebo; Q2W = every 2 weeks; Q4W = every 4 weeks; Q8W = every 8 weeks; n/N = number of responders/total number of patients; OR = odds ratio; RR = risk ratio; RD = risk difference; CI = confidence interval

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

6.31 The point estimates of the odds ratios (ORs) for attack-free patients (i.e., the relative odds or relative likelihood of being attack free) numerically favoured the comparators LANA Q2W, LANA Q4W, and GARA Q4W over DONI Q4W (DONI vs. comparator ORs: 0.57, 0.40, and 0.14, respectively). The evaluation considered that the ITC results for attack-free patients were uncertain given the small patient numbers in the trials, the low event counts and that the event rates in the 'common reference' PBO arms differed across the trials (e.g., 2/22 [9.1%] for OASIS-HAE, 1/41 [2.4%] for HELP and 0/25 for VANGUARD).

6.32 The PBAC also noted the HAE attack rates in the placebo arms of each of the trials were based on 0, 1 or 2 individuals who experienced an attack. Overall, the PBAC acknowledged that interpretation of the comparative effectiveness data should recognise the rare nature of HAE.

Comparative harms

DONI versus PBO

6.33 Table 9 summarises the overall TEAE in the DONI and PBO arms of OASIS-HAE for the full treatment period.

Table 9: OASIS-HAE - Overall summary of TEAEs (SAS)

	DONI 80 mg Q4W (N = 45)	DONI 80 mg Q8W (N = 23)	PBO (N=22)
Any AE, n (%)	33 (73.3)	15 (65.2)	19 (86.4)
Any TEAEs, n (%)	33 (73.3)	14 (60.9)	18 (81.8)
Any TEAE related to study treatment, n (%)	19 (42.2)	4 (17.4)	6 (27.3)
Any TEAE leading to discontinuation, n (%)	1 (4.3)	1 (4.3)	0
Any TEAE leading to discontinuation related to study treatment, n (%)	0	1 (4.3)	0
Any SAE, n (%)	0	0	1 (4.5)
Any SAE related to study treatment, n (%)	0	0	0

Source: Table 45, p102 of the submission.

AE = adverse event; DONI = donidalorsen; HAE = hereditary angioedema; PBO = placebo; SAS = safety analysis set; Q4W = every 4 weeks; Q8W = every 8 weeks; SAS = safety analysis set; TEAE = treatment-emergent adverse event

In OASIS-HAE, 33 patients (73.3%) in the DONI Q4W arm and 19 patients (86.4%) in the PBO arm experienced at least one TEAE. Of these, 19 patients (42.2%) and 6 patients (27.3%) in the in the DONI Q4W and PBO arms, respectively, experienced a TEAE considered by the trial investigators to be drug related.

6.34 Overall, treatment-related TEAEs were uncommon, generally mild, and limited primarily to local injection site reactions and headache. Six patients (13.3%) in the DONI Q4W arm experienced injection site erythema. Three patients (6.7%) in the DONI Q4W arm experienced each of the following TEAEs considered related to the study drug: headache, injection site discolouration, injection site pruritus, and injection site pain.

6.35 Any interpretation of the safety results in OASIS-HAE should consider the small number of patients included in the clinical trial.

ITCs: DONI versus LANA and DONI versus GARA

6.36 An ITC of TEAEs between DONI Q4W, LANA Q2W and Q4W, and GARA Q4W is presented in Table 10.

Table 10: ITC of number of TEAEs during the full treatment periods for the active comparators

OASIS-HAE DONI arms	HELP for LANA arms VANGUARD for GARA arm	DONI vs PBO, OR [95% CI]	Active comparators vs PBO, OR [95% CI]	DONI vs active comparators, OR [95% CI]; (nominal p-value)
DONI Q4W	LANA Q2W	0.61 [0.17, 2.17]	8.39 [1.01, 69.92]	**0.07 [0.01, 0.86]; 0.0377**
	LANA Q4W		2.02 [0.56, 7.21]	0.30 [0.05, 1.83]; 0.1932
	GARA Q4W		1.19 [0.42, 3.35]	0.51 [0.1, 2.65]; 0.4253

Source: Table 57, p123 of the submission.

CI = confidence interval; DONI = donidalorsen; GARA = garadacimab; HAE = hereditary angioedema; ITC = indirect treatment comparison; LANA = lanadelumab; OR = odds ratio; Q2W = every 2 weeks; Q4W = every 4 weeks; TEAEs = treatment emergent adverse events.

Notes: OR estimates <1 favour DONI

Bolded = statistical significance (analysis was not powered to detect statistical significance and no adjustment of multiplicity was undertaken).

6.37 As for effectiveness, the ITC of safety results lacked precision with very wide 95% CIs and the analyses of AE outcomes were not statistically powered. In addition, the evaluation considered that the 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

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

Clinical claim

6.39 The submission presented clinical claims for both the DONI Q4W and DONI Q8W dosing regimens.

6.40 The submission described DONI Q4W as:

- non-inferior in terms of efficacy and safety relative to LANA Q2W and Q4W as a LTP treatment of HAE attacks.
- non-inferior in terms of efficacy and safety relative to GARA Q4W as a LTP treatment of HAE attacks.

6.41 The evidence was based on anchored ITCs involving small patient numbers. The evaluation considered that there were some transitivity issues between the included trials which may have resulted in unreliable indirect estimates of treatment effect. Further, the evaluation considered that the inherent variability and unpredictability in HAE attacks also added uncertainty to the ITCs. Based on the results of the primary ITC of time-normalised HAE attacks using the full treatment period in OASIS-HAE (Week 1-Week 25) and the secondary analyses (Week 5 to Week 25), the ESC considered that the claim of non-inferior comparative effectiveness was reasonable. Overall, the ESC considered that the ITC analysis of safety was generally supportive of the clinical claim, noting that longer term safety data were not available (see paragraph 6.45). The evaluation and the ESC considered that interpretation of the comparative effectiveness and safety data should recognise the rare nature of HAE.

6.42 The submission described DONI Q8W as:

- non-inferior in terms of efficacy and safety relative to LANA Q2W and Q4W as a LTP treatment of HAE attacks.
- non-inferior in terms of efficacy and safety relative to GARA as a LTP treatment of HAE attacks

6.43 The submission stated that i) this is reflective of the effect size following achievement of maximum treatment effects as demonstrated in OASIS-HAE and OASISplus, and ii) this takes into account the circumstances of use expected for this regimen in the PBS setting—namely, that Q4W is required as the initiation dose, with subsequent down-titration to Q8W permitted once sustained response to Q4W has been established.

6.44 The PI recommends the DONI Q8W regimen only if the condition is well controlled (e.g., attack-free) for at least 3 months with the Q4W regimen. However, no indirect comparisons were presented between the trials whereby the DONI Q8W represented a down titration arm from DONI Q4W. The DONI Q8W arm was an initiation arm in the key OASIS-HAE trial and hence, has limited applicability to clinical practice. The ESC agreed that this issue remains an area of uncertainty but noted the initiation data from this arm of the trial supported the possibility that some patients may be adequately controlled with less frequent DONI dosing. The pre-PBAC response stated that the option of Q8W dosing represented an important source of flexibility for clinicians and patients.

6.45 DONI therapy is likely to be ongoing in many patients. The evaluation noted the lack of long-term efficacy and safety data for DONI, given the limited treatment duration in clinical studies, e.g., the maximum follow-up duration provided from the non-comparative OASISplus open-label extension (OLE) study was 52 weeks.

6.46 The PBAC considered that the claim of non-inferior comparative effectiveness and safety (versus lanadelumab and garadacimab) was adequately supported by the data.

Economic analysis

6.47 The submission presented three CMAs (Approaches 1, 2 and 3) to support the listing of DONI for the LTP of recurrent HAE attacks. The key components and assumptions of the CMAs are presented in Table 11.

Table 11: Key components and assumptions of the cost-minimisation approach

Component	Claim or assumption
Therapeutic claim: effectiveness	Based on evidence presented above, effectiveness was claimed to be non-inferior.
Therapeutic claim: safety	Based on evidence presented above, safety was claimed to be non-inferior.
Evidence base	Indirect comparison of DONI (OASIS-HAE trial) and LANA (HELP trial).
Equi-effective doses	The submission presented three CMAs to account for the different dosing regimens of LANA. All approaches used a four-week time horizon. Approach 1: 80 mg of DONI is equivalent to 300 mg of LANA over four weeks. This was considered to be the base case. Approach 2 and 3: 80 mg of DONI is equivalent to 480 mg of LANA over four weeks.
Direct medicine costs	The costs per patient per month were equivalent based on the equi-effective doses presented above.
Other costs or cost offsets	No other costs were included given the similarity in administration and the claim of non-inferior safety in the submission. Refer to the comparative harms section for discussion.

Source: Constructed during the evaluation from Section 3 of the submission
CMA = cost-minimisation approach, DONI = donidalorsen; LANA = lanadelumab.

6.48 The submission presented three CMA approaches because LANA 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. The RSA for lanadelumab intends to account for this risk (along with other risks, refer to paragraph 6.64), thus the submission raised concerns that LANA would disproportionately consume more of the RSA expenditure cap than DONI (due to

patients receiving more frequent dosing than Q4W for LANA). The three CMA approaches represented different ways to help ensure that DONI would not be adversely affected by the risk of more frequent LANA dosing (noting the GARA PSD was not published at the time the submission was prepared).

6.49 The evaluation considered Approach 1, where DONI Q4W was compared with LANA Q4W, as the base case. This approach assumed that DONI 80 mg Q4W is equi-effective to LANA 300 mg Q4W. This was consistent with the ESC's consideration of GARA in November 2025 where it was stipulated that the CMA should compare GARA to LANA Q4W, as that reflected the basis upon which the PBAC recommended that LANA would be cost-effective (paragraph 7.8, GARA PSD, November 2024 PBAC meeting). The ESC considered that Approach 1 was the most appropriate base case. In its consideration of GARA, the PBAC had advised that the sponsor and Department may consider the actual LANA dosing frequency in clinical practice, in the context of GARA joining the existing RSA (refer to paragraph 7.9) while ensuring that the cost of GARA is no higher than LANA.

6.50 For the alternative approaches (2 and 3), DONI Q4W dosing was compared against the real-world utilisation of LANA (1.6 vials [480 mg] per 34 days) based on a Drug Utilisation Section (DUS) analysis. In Approach 2 the unit price of LANA was reduced so that the average treatment cost for four weeks was equal to the published LANA vial price. For Approach 3 the full LANA unit cost was applied.

6.51 The CMAs were conducted over a four-week duration. This was appropriate as neither DONI nor LANA require a loading dose. No other costs or cost-offsets were considered. The ESC considered that this was reasonable.

6.52 The results of CMAs based on three approaches are presented in Table 12. In each approach the DONI unit price (one vial per four weeks) was matched to the four-week LANA treatment cost. These CMAs were based on the published ex-manufacturer price for LANA ($18,440 per 300 mg injection).

Table 12: Results of the three CMA approaches, based on the published price for LANA

	Base case		Alternative approaches			
	Approach 1		Approach 2		Approach 3	
	DONI	LANA	DONI	LANA	DONI	LANA
Dosing schedule	Q4W	Q4W	Q4W	Q2W for 60% and Q4W for 40% of patients[a]	Q4W	Q2W for 60% and Q4W for 40% of patients[a]
Vials per 4 weeks	1	1	1	1.6[b]	1	1.6[b]
Cost per vial	$18,440	$18,440[c]	$18,440	$11,525[d]	$29,504	18,440[c]
Total cost per 4 weeks	$18,440	$18,440	$18,440	$18,440 (because LANA price reduced)	$29,504	$29,504
RSA changes	Adjust rebate distribution to apply less weight on DONI expenditure.		Nil			

Source: Constructed during the evaluation from the "Section 3 DONIDALORSEN CMA" Excel spreadsheet provided with the submission and the "Section 4 DONIDALORSEN BIM" Excel Workbook included with the submission.
AEMP = approved ex-manufacturer price; DONI = donidalorsen; DUS = Drug Utilisation Section; LANA = lanadelumab; PI = product information; Q2W = every two weeks; Q4W = every four weeks; RSA = risk-sharing arrangement
[a] The submission provided a commissioned DUS analysis which indicated the mean vials per dispense of LANA was 1.6. This suggests that the distribution of dosing was 60% for Q2W and 40% Q4W.
[b] Q2W dosing regimen requires two vials per four weeks while Q4W requires one vial. The weighted average number of vials per four weeks is therefore 1.6 vials.
[c] Published AEMP for lanadelumab.
[d] The submission has back calculated the price per vial so that the cost of 1.6 vials every four weeks would equal the published LANA vial price ($18,440).

6.53 A CMA was conducted during the evaluation between DONI and GARA. It utilised a two-year time horizon given that GARA requires a loading dose. The equi-effective doses were calculated as DONI 2,087 mg (80 mg Q4W x 26.1 doses) and GARA 5,000 mg (400 mg as loading dose + 200 mg per month x 23 doses) over two years. The dose of GARA over two years, i.e. 5,000 mg, was previously accepted by the PBAC for the CMA of LANA versus GARA (paragraph 7.7, GARA PSD, November 2024 PBAC meeting). The PSCR and pre-PBAC response were supportive of this approach.

Drug cost/patient/year

6.54 The drug cost per patient per year is presented in Table 13 based on published prices.

Table 13: Drug cost per patient for DONI and LANA (based on published prices)

	DONI			LANA		
	Trial OASIS-HAE	CMA	Financial estimates	Trial HELP Study	CMA	Financial estimates
Mean dose per 4 weeks (vials)	79.12mg[a] (0.99 vial)	80 mg (1 vial)		441.97mg[b] (1.5 vials)	300 mg (1 vial)	480 mg (1.6 vials)
Cost per dose	$18,237	$18,440	$18,603	$27,167	$18,440	$29,667
Cost/patient/month	$19,757	$19,977	$20,153	$29,431	$19,977	$32,139
Cost/patient/year	$237,084	$239,721	$241,839	$353,165	$239,721	$385,672

Source: Constructed during the evaluation from the "Section 3 DONIDALORSEN CMA" excel spreadsheet provided with the submission.
CMA = cost-minimisation approach; DONI = donidalorsen; LANA = lanadelumab
[a] Mean dose reported in the OASIS-HAE trial was 474.7 mg over 24-week study duration.

[b] Mean weighted dose calculated from the Q2W and Q4W cohorts in the HELP study, with a compliance rate of 99%, reported in Banerji et al. (2018).[17]

6.55 DONI costs were generally consistent across the trial, the CMA (based on Approach 1) and the financial estimates (noting that dispensing fees are added to the financial estimates). For LANA, the trial assumed 1.5 vials Q4W, the CMA assumed 1 vial and the financials assumed 1.6 vials. The observed utilisation of LANA (based on a DUS analysis) is 1.6 vials Q4W.

Estimated PBS usage & financial implications

6.56 This submission was not considered by DUSC. A market-share approach was used to estimate the size of the existing LANA HAE market. An epidemiological approach was used to estimate the number of HAE patients treated with C1-INH who would switch to DONI. The submission presented three different financial estimates based on the three CMA approaches. The evaluation focussed on Approach 1, with Approaches 2 and 3 presented as sensitivity analyses.

6.57 Key inputs for the financial estimates are presented in Table 14.

Table 14: Key inputs for financial estimates

Parameter	Value	Source	Comment
Market: Chronic treatment of HAE			
Existing market	1,599[1] LANA scripts in 2025	Utilisation for LANA (PBS item 12790E)	The evaluation considered that, given the restriction requested in the submission included a shorter duration of eligibility assessment, there may be some market growth from less severe HAE patients. However, the PBAC considered the duration of eligibility assessment should remain unchanged (refer to para 7.3).
% growth rate	Year 1: 7.63%, Year 2: 3.54%, Year 3: 3.42%, Year 4: 3.31%, Year 5: 3.20%, Year 6: 3.10%	Derived using LANA script growth between 2024-2025 (61 scripts). The submission assumed an increase of 61 scripts in each future year.	The submission considered that, as utilisation had essentially plateaued, increasing the script number by 61 each year was an appropriate approach. The evaluation considered that, if the market is at steady-state, a more appropriate approach may be to apply the ABS population growth rate. Alternatively, given sufficient historical dispensing data are available, the market growth rate could be derived by graphing the historical data, adding a trendline and using its equation to project future growth.
DONI uptake rate	[redacted]% in Year 1, increasing to [redacted]% in Year 6.	Sponsor assumption.	The evaluation considered this was uncertain. Although the dosing schedule of DONI may result in less frequent dosing for some patients which may increase uptake, the recent listing of GARA may result in reduced uptake.

[17] Banerji A, Riedl MA, Bernstein JA, et al. Effect of Lanadelumab Compared With Placebo on Prevention of Hereditary Angioedema Attacks: A Randomized Clinical Trial. JAMA. 2018;320(20):2108–2121. doi:10.1001/jama.2018.16773

Parameter	Value	Source	Comment
Script equivalence	1:1	Assumed that both scripts would last for four weeks. The PSCR stated that the assumption of 1:1 script equivalence meant that compliance and treatment continuation rates were implicitly assumed to be the same between DONI and LANA.	Assumes both DONI and LANA are dosed Q4W. Data from DUS[a] indicates that the mean time between LANA scripts was 34 days in 2025, resulting in an equivalence of 1.2:1. The PSCR stated the observed mean time between LANA scripts of 34 days (vs 28 days based on a strict Q4W regimen) is reflective of compliance and dispensing behaviour generally observed with LTP treatments of this nature. The PSCR stated that patients treated with LANA on the PBS received, on average, 1.6 vials per dispensing to accommodate a more frequent treatment interval than Q4W (see LANA cost per script below).
Population: HAE patients treated with C1-INH			
C1-INH treated population	100 patients each year	NBA C1-INH Utilisation Review[18]	The evaluation considered this was reasonable.
DONI uptake rate	[redacted]% in Year 1 increasing to [redacted]% in Year 6	Proportion switching from C1-INH to GARA (Table 13, GARA PSD, November 2024 PBAC meeting). This would equate to [redacted][2] patients switching in Year 1, a total of [redacted][2] patients having switched from C1-INH by Year 2 (i.e. [redacted][2] additional patient would switch in Year 2), a total of [redacted][2] patients by Year 3 (i.e. [redacted][2] additional patient would switch in Year 3) etc. The submission estimated that a total of [redacted][2] patients would switch from C1-INH to donidalorsen (who are unable to use lanadelumab and garadacimab) over the 6 year period.	The evaluation considered this may be an overestimate given these patients also have GARA and LANA as treatment options. The PBAC considered that uptake from patients who would otherwise be treated with C1-INH would be small given donidalorsen would be the third drug listed for this condition, and that the submission's assumptions seemed reasonable.
Proposed medicine: DONI			
Cost per script	Approach 1 = $18,603 (Approach 2 = $18,603; Approach 3 = $29,667)	CMA derived costs with Section 85 dispensing fees, assuming one vial every four weeks for DONI.	-
Affected products: LANA and C1-INH			
LANA cost per script	Approach 1 = $29,667 (Approach 2 = $18,603; Approach 3 = $29,667).	1.6 vials per script was assumed, based on the real-world utilisation of LANA.[a]	Although this was inconsistent with the CMA approach which applied 1 LANA vial per script, the evaluation considered it may be reasonable given that 1.6 vials per script is the actual observed utilisation of LANA.

[18] https://www.blood.gov.au/sites/default/files/documents/2024-07/PDF%20C1-INH%20Review%20Report%20-%20FV%20Executive%20summary.pdf

Parameter	Value	Source	Comment
C1-INH cost per patient per year	$463,534	Dosing regimen (60 IU/kg, twice a week, reported in C1-INH utilisation report[18] × average weight (70 kg, assumed) × cost ($2,122.41 per 2,000 IU vial, reported in 2022 NBA Annual Report[19]).	The evaluation considered that the weight of patients using C1-INH is uncertain; this parameter was tested in sensitivity analyses.

Source: Constructed during the evaluation from the "Section 4 DONIDALORSEN BIM" Excel Workbook included with the submission.
ABS = Australian Bureau of Statistics; CMA = cost-minimisation approach; C1-INH = C1-esterase inhibitor; DONI = donidalorsen; DUS = Drug Utilisation Section; GARA = garadacimab; IU = international units; LANA = lanadelumab; NBA = National Blood Authority; PBAC = Pharmaceutical Benefits Advisory Committee; PBS = Pharmaceutical Benefits Scheme; PSD = Public Summary Document; Q2W = every two weeks; Q4W = every four weeks

[a] The submission provided a commissioned DUS analysis which indicated the average number of vials dispensed per LANA script was 1.6 and the average time between scripts was 34 days in 2025.

The redacted values correspond to the following ranges:

[1] 500 to < 5,000

[2] < 500

6.58 The net financial implications to the PBS are presented in Table 15. Based on the use of LANA, the submission assumed that there would be no use of DONI on the RPBS.

Table 15: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
C1-INH switching patients	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1
DONI scripts from patients who switched from C1-INH [b]	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1
DONI scripts from patients who switched from LANA[a]	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]2	[redacted]2
Total number of scripts dispensed	[redacted]1	[redacted]1	[redacted]1	[redacted]2	[redacted]2	[redacted]2
Cost to the PBS for DONI ($)	[redacted]3	[redacted]3	[redacted]3	[redacted]3	[redacted]4	[redacted]4
PBS offsets for reduce use of LANA ($)	-[redacted]5	-[redacted]5	-[redacted]5	-[redacted]5	-[redacted]5	-[redacted]5
Net financial implications to the PBS ($)	-[redacted]5	-[redacted]5	-[redacted]5	-[redacted]5	-[redacted]5	-[redacted]5
Cost savings for the NBA ($)	-[redacted]5	-[redacted]5	-[redacted]5	-[redacted]5	-[redacted]5	-[redacted]5
Net financial implications to the health budget ($)	-[redacted]5	-[redacted]5	-[redacted]5	-[redacted]5	-[redacted]5	-[redacted]5

Source: Constructed during the evaluation from the "Section 4 DONIDALORSEN BIM" Excel Workbook included with the submission.
C1-INH = C1-esterase inhibitor; DONI = donidalorsen; LANA = lanadelumab; NBA = National Blood Authority; PBS = Pharmaceutical Benefits Scheme

Note: The submission assumed no RPBS utilisation.

[a] Assuming 13 scripts per year as estimated by the submission.

[b] These are patients who switched from C1-INH at any point over the financial estimates (i.e. only 10 patients were estimated to have switched over the total 6-year period).

The redacted values correspond to the following values:

[1] < 500

[2] 500 to < 5,000

[3] $0 to < $10 million

[4] $10 million to < $20 million

[5] net cost saving

[19] https://www.transparency.gov.au/publications/health/national-blood-authority/national-blood-authority-annual-report-2021-22/

6.59 The net cost to the PBS of listing DONI was estimated to be a cost saving of $10 million to < $20 million using Approach 1. The cost saving to the PBS was because the submission based the cost of LANA on 1.6 vials per script (and assumed 1:1 script equivalence).

6.60 The submission also estimated a cost saving for the NBA due to reduced use of C1-INH. The ESC, noting that DONI is the third drug for the treatment of HAE, considered that the cost savings to the NBA may not be realised in clinical practice. Refer to paragraph 7.13 for the PBAC's advice.

6.61 The ESC considered that the overall intent would be for the listing of DONI to be approximately cost neutral to the PBS once the confidential effective prices and the impact of RSA rebates for the use of LANA Q2W were taken into account; with the exception of the group of patients anticipated to switch from C1-INH (the submission estimated this would be 5 patients in Year 1 and a total 10 patients over the 6-year period). The ESC noted that there may be a small saving to the PBS if a proportion of patients receive DONI Q8W (rather than Q4W) but considered that the potential uptake of the regimen was unclear.

6.62 Financial estimates based on CMA Approaches 2 and 3 are presented as sensitivity analyses. The submission presented additional sensitivity analyses varying the proportion of DONI patients who would receive a Q8W dosing regimen. Sensitivity analyses were also conducted during the evaluation (see Table 16).

Table 16: Sensitivity analyses on the net financial impact to the PBS and the health budget with Approach 1

		2027	2028	2029	2030	2031	2032	%
Base case	**PBS**	**-$[redacted][1]**	**-$[redacted][1]**	**-$[redacted][1]**	**-$[redacted][1]**	**-$[redacted][1]**	**-$[redacted][1]**	**[redacted]%**
	Health Budget	**-$[redacted][1]**	**-$[redacted][1]**	**-$[redacted][1]**	**-$[redacted][1]**	**-$[redacted][1]**	**-$[redacted][1]**	**[redacted]%**
CMA Approach (base case: Approach 1)								
Approach 2	PBS	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	-[redacted]%
	Health Budget	-$[redacted][1]	-$[redacted][1]	-$[redacted][1]	-$[redacted][1]	-$[redacted][1]	-$[redacted][1]	[redacted]%
Approach 3	PBS	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	-[redacted]%
	Health Budget	-$[redacted][1]	-$[redacted][1]	-$[redacted][1]	-$[redacted][1]	-$[redacted][1]	-$[redacted][1]	[redacted]%
Proportion of DONI patients with Q8W dosing regimen (base case: 0%)								
20%	PBS	-$[redacted][1]	-$[redacted][1]	-$[redacted][1]	-$[redacted][1]	-$[redacted][1]	-$[redacted][1]	[redacted]%
	Health Budget	-$[redacted][1]	-$[redacted][1]	-$[redacted][1]	-$[redacted][1]	-$[redacted][1]	-$[redacted][1]	[redacted]%
40%	PBS	-$[redacted][1]	-$[redacted][1]	-$[redacted][1]	-$[redacted][1]	-$[redacted][1]	-$[redacted][1]	[redacted]%
	Health Budget	-$[redacted][1]	-$[redacted][1]	-$[redacted][1]	-$[redacted][1]	-$[redacted][1]	-$[redacted][1]	[redacted]%
DONI uptake rate from C1-INH (base case: [redacted]% - [redacted]%[d])								
[redacted]%	PBS	-$[redacted][1]	-$[redacted][1]	-$[redacted][1]	-$[redacted][1]	-$[redacted][1]	-$[redacted][1]	[redacted]%
	Health Budget	-$[redacted][1]	-$[redacted][1]	-$[redacted][1]	-$[redacted][1]	-$[redacted][1]	-$[redacted][1]	-[redacted]%
DONI : LANA script replacement rate (base case: 1:1)								
1.2:1	PBS	-$[redacted][1]	-$[redacted][1]	-$[redacted][1]	-$[redacted][1]	-$[redacted][1]	-$[redacted][1]	-[redacted]%
	Health Budget	-$[redacted][1]	-$[redacted][1]	-$[redacted][1]	-$[redacted][1]	-$[redacted][1]	-$[redacted][1]	-[redacted]%

Source: Constructed during the evaluation from the "Section 4 DONIDALORSEN BIM" Excel Workbook included with the submission.
ABS = Australian Bureau of Statistics; CMA = cost-minimisation approach; C1-INH = C1-esterase inhibitor; DONI = donidalorsen; IU = international units; NBA = National Blood Authority; PBS = Pharmaceutical Benefits Scheme; Q8W = every eight weeks.

The redacted values correspond to the following ranges:
[1] net cost saving
[2] $0 to < $10 million

6.63 The above sensitivity analyses assume no market growth is associated with listing DONI on the PBS (other than patients transitioning from C1-INH treatment).

Financial Management – Risk Sharing Arrangements

6.64 The submission stated that, if recommended, DONI would join the current RSA with LANA (and GARA). The LANA RSA was intended to: (a) account for the risk of higher dosing frequency (i.e. Q2W); (b) manage the risk of use in cost-ineffective populations; and (c) achieve cost-effectiveness for the listing. However, if CMA Approach 1 (see paragraph 6.48) is accepted by the PBAC, the submission stated that an adjustment factor, that takes into account the real-world utilisation of LANA, would be required to fairly allocate rebate responsibility as the assumed 1:1 dose relativity between DONI Q4W and LANA Q4W does not reflect observed clinical practice (as LANA is used more frequently than Q4W in clinical practice). The submission stated, with its more frequent dosing, LANA would disproportionately consume more of the expenditure threshold.

6.65 This issue was also noted in the PBAC's consideration of GARA (which has joined the LANA RSA) and were highlighted in the PSCR for DONI. In its consideration of GARA, the PBAC noted that the risk of a higher dosing frequency was not relevant to GARA, but the other risks were relevant and should be managed within the RSA. The PBAC further advised that the "the sponsor of garadacimab should not be adversely affected by the risk of more frequent lanadelumab dosing" (paragraph 7.10, GARA PSD, November 2024 PBAC meeting).

6.66 In its consideration of GARA, the PBAC also recommended a small increase in the expenditure thresholds to account for patients who were treated with C1-INH who switched to GARA (paragraph 7.11, GARA PSD, November 2024 PBAC Meeting). Following the recent listing of GARA and its inclusion in the RSA, the ESC noted that further changes to the expenditure thresholds may not be necessary if DONI is recommended.

6.67 The PSCR and pre-PBAC response requested equivalent pricing and RSA arrangements to GARA.

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 donidalorsen 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 donidalorsen would be acceptable if it were cost-minimised to the lowest cost alternative therapy of garadacimab or lanadelumab. The PBAC advised that donidalorsen should join the existing risk sharing arrangement (RSA) with similar arrangements to garadacimab.

7.2 The PBAC noted and welcomed the input from individuals, health professionals and organisations via the Consumer Comments facility. The comments highlighted the value of an additional long-term prophylaxis option, noting that patients may respond differently to different therapies and that the distinct mechanism of action, pre-filled pen device and potential for less frequent dosing with donidalorsen may support more individualised treatment.

7.3 The PBAC advised the restriction should align with existing PBS restrictions for garadacimab and lanadelumab, including maintaining the current HAE attack-frequency threshold of ≥ 12 treated acute HAE attacks in the preceding 6 months. The PBAC noted the submission requested a shorter assessment timeframe. However, the PBAC considered this may allow patients with a lower level of baseline risk to access long-term prophylaxis and noted that previous assessments had found cost-effectiveness to be highly sensitive to baseline attack frequency. Further, while the TGA indication would enable use in Type 3 HAE, the PBAC considered there was insufficient evidence to support the cost-effectiveness of donidalorsen in this subtype, given: the economic model for lanadelumab in HAE was applicable only to Types 1 and 2 HAE; and Type 3 has less clearly defined diagnostic criteria and so represents a more difficult to define target population.

7.4 The PBAC considered that the nominated comparators, lanadelumab and garadacimab, were appropriate.

7.5 The PBAC noted the submission was supported by one randomised controlled trial (RCT) that compared donidalorsen with placebo (OASIS-HAE). In OASIS-HAE, donidalorsen (4-weekly) was associated with an 81% reduction (95% CI: -89.3%, -64.9%) in the rate of HAE attacks from Week 1 to Week 25 relative to placebo (least square mean, per 4 weeks). The submission's claim of non-inferior comparative effectiveness and safety was based on an indirect comparison between the OASIS-HAE trial and the key trials of lanadelumab versus placebo (HELP), and garadacimab versus placebo (VANGUARD). The PBAC noted the indirect comparison found that the time-normalised number of HAE attacks per month numerically favoured donidalorsen (administered 4-weekly) compared with lanadelumab (2-weekly or 4-weekly). The indirect comparison showed similar efficacy estimates for donidalorsen and garadacimab (both administered 4-weekly). The PBAC acknowledged the limitations of the analyses including the small patient numbers, wide confidence intervals and transitivity issues but interpreted the evidence in the context of HAE being a rare condition. Overall, the PBAC accepted the claim of non-inferior comparative effectiveness versus lanadelumab and garadacimab.

7.6 The PBAC also considered the claim of non-inferior comparative safety (versus lanadelumab and garadacimab) was reasonable but acknowledged it was limited by small patient numbers and the relatively short duration of follow-up data.

7.7 The TGA Product Information stated that an 8-weekly (2-monthly) dosing interval may be considered in patients who are well controlled for at least 3 months while receiving donidalorsen. The PBAC noted the lack of clinical trial data involving down-titration to the 8-weekly dose but considered the available data (in which the 8-weekly regimen was used from initiation) supported the possibility that some patients may be adequately controlled with this less frequent dosing. The PBAC considered the 8-weekly regimen would enable flexibility for patients and clinicians.

7.8 The PBAC considered that listing on a cost-minimisation basis versus lanadelumab and garadacimab was reasonable. The PBAC considered the equi-effective doses versus lanadelumab should be:

- donidalorsen 80 mg every 4 weeks; and
- lanadelumab 300 mg every 4 weeks.

7.9 The PBAC acknowledged the sponsor's concerns regarding the more frequent dosing of lanadelumab in clinical practice but considered that the equi-effective dose should reflect the basis on which lanadelumab was originally accepted as cost-effective (i.e. 4-weekly dosing) and be consistent with the approach previously applied to garadacimab. In its consideration of garadacimab 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 while ensuring that the cost of garadacimab is no higher than lanadelumab" (paragraph 7.8, garadacimab PSD, November 2024 PBAC meeting), refer to paragraph 7.12.

7.10 The PBAC considered the equi-effective dose versus garadacimab should be calculated over a 2-year period from the initiation of treatment and should include the garadacimab loading dose, consistent with the approach used in the CMA of garadacimab versus lanadelumab (paragraph 7.6, garadacimab PSD, November 2024 PBAC meeting). The PBAC considered the equi-effective doses over two years should be:

- donidalorsen 2,087 mg (based on 80 mg every 4 weeks, and 26.09 vials over two years); and
- garadacimab 5,000 mg (based on 200 mg every month (23 vials) plus a loading dose of 400 mg, i.e. a total of 25 vials).

7.11 The PBAC considered that the submission's approach to estimating utilisation was reasonable. The PBAC noted that, once confidential prices and RSA arrangements are taken into account, the overall intent would be for the listing to be broadly cost neutral to the PBS, except for the group of patients anticipated to switch from C1-INH (refer to paragraph 7.13). The PBAC noted that while this group would be associated with a cost to the PBS, there would be a cost-saving to the NBA due to reduced use of C1-

INH. The PBAC considered that any savings associated with less frequent dosing of donidalorsen (i.e. the 8-weekly regimen) were uncertain and likely very small, and thus considered the submission's approach of excluding this from the financial estimates was reasonable.

7.12 The PBAC considered donidalorsen should join the existing HAE RSA, with similar arrangements to garadacimab. The PBAC considered the following risks/issues, which are currently managed in the lanadelumab and garadacimab RSA, are relevant to donidalorsen and should be managed within an RSA: (a) use in cost-ineffective populations; and (b) achieve cost-effectiveness for the listing. The PBAC considered that the other risk accounted for in the lanadelumab RSA, the risk of higher dosing frequency, was not relevant to donidalorsen. Thus, consistent with its consideration of garadacimab, the PBAC advised that the sponsor of donidalorsen should not be adversely affected by the risk of more frequent lanadelumab dosing.

7.13 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 donidalorsen (i.e. who are unable to use lanadelumab or garadacimab). The PBAC considered this number would be small given donidalorsen would be the third drug listed for this condition.

7.14 With regards to the proposed restrictions, the PBAC recommended the following:

- An Authority Required (Written) for the initial listings (Initial 1, 2 and 3) and Authority Required (Telephone/Online) for the continuing listing
- A maximum quantity of 1 unit and 5 repeats across all initial and continuing listings would be reasonable, as proposed in the submission.
- The restriction should allow flexibility for dosing to be titrated within a 6-month period.
- In patients switching from C1-INH, the restriction should allow C1-INH to be continued when commencing donidalorsen (noting the Product Information states C1-INH should be continued for 14 days after initiating donidalorsen).
- An age-agnostic listing to align with lanadelumab and garadacimab listings.
- Switching should be permitted from lanadelumab or garadacimab to donidalorsen (the 'Initial 3 restriction'). The PBAC also advised that flow-on changes would be required to the lanadelumab and garadacimab restrictions to allow switching and to prevent combination use of these three therapies.
- Clinical criterion stipulating that medical practitioners should request the appropriate number of repeats to provide for a continuing course of up to 24 weeks of therapy to ensure patients who are on the reduced dose (80 mg every 8 weeks) are re-assessed every six months
- Addition of the standard 'no increases' clauses as the dosing and administration information in the TGA-approved Product Information does not suggest flexibility for additional doses is required.

- The PBAC noted the submission did not request a grandfather restriction

7.15 The PBAC recommended that donidalorsen, garadacimab and lanadelumab should be treated as interchangeable, under s101(3BA) of the *National Health Act 1953*.

7.16 The PBAC advised that donidalorsen is not suitable for prescribing by nurse practitioners.

7.17 The PBAC advised that donidalorsen should not be exempt from the Early Supply Rule as it currently applies to lanadelumab and garadacimab.

7.18 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because donidalorsen is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over lanadelumab or garadacimab, or not expected to address a high and urgent unmet clinical need given the presence of alternative therapies, 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:

MEDICINAL PRODUCT **medicinal product pack**	**PBS item code**	**Max. qty packs**	**Max. qty units**	**№.of Rpts**	**Available brands**
DONIDALORSEN					
donidalorsen 80 mg/0.8 mL, 1 x 0.8 mL pen device	NEW	1	1	5	Zirdawny
Restriction Summary / Treatment of Concept					
Category / Program: ☒ GENERAL - General Schedule (Code GE)					
Prescriber type: ☒Medical Practitioners					
Restriction type: ☒Authority Required (FULL assessment) in writing only via post/HPOS upload/Online PBS Authorities)					
Administrative Advice: No increase in the maximum number of repeats may be authorised					
Administrative Advice: No increase in the maximum number of units may be authorised					
Administrative Advice: Special Pricing Arrangements apply.					
Indication: Chronic treatment of hereditary angioedema Types 1 or 2					
Treatment Phase: Initial 1: New patient (commencing with no previous treatment with C1-INH for routine prophylaxis)					
Clinical criteria:					
Patient must have experienced at least 12 treated acute attacks of hereditary angioedema within the 6 month period prior to commencing treatment with this drug					
AND					

Clinical criteria:
Patient must not have been receiving a C1-esterase inhibitor through the National Blood Authority as routine prophylaxis for hereditary angioedema at the time of application
AND
Clinical criteria:
The treatment must not be used in combination with any of: (i) C1-esterase inhibitor concentrate (ii)–lanadelumab (iii) garadacimab
Treatment criteria:
Must be treated by a clinical immunologist or a specialist allergist
Prescribing Instructions: For the purposes of administering this restriction, acute attacks of hereditary angioedema are those of a severity necessitating immediate medical intervention with either: (i) icatibant, or (ii) C1-esterase inhibitor concentrate
Prescribing Instructions: The baseline measurement of the number of treated acute attacks of hereditary angioedema within the 6 months prior to initiating treatment must be provided at the time of submitting this application
Administrative Advice: Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au. Applications for authorisation under this restriction should be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/hpos) Alternatively, applications for authority to prescribe can be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos Or mailed to: Services Australia Complex Drugs Reply Paid 9826 HOBART TAS 7001
Restriction Summary / Treatment of Concept
Category / Program: ☒ GENERAL - General Schedule (Code GE)
Prescriber type: ☒Medical Practitioners
Restriction type: ☒Authority Required (FULL assessment) in writing only via post/HPOS upload/Online Authorities)
Indication: Chronic treatment of hereditary angioedema Types 1 or 2
Treatment Phase: Initial 2: New patient (commencing from National Blood Authority-funded C1-INH)
Clinical criteria:
Patient must have been receiving a C1-esterase inhibitor through the National Blood Authority as routine prophylaxis for hereditary angioedema immediately prior to receiving this drug
AND
Clinical criteria:
The treatment must not be used in combination with any of: (i) C1-esterase inhibitor concentrate, unless the combination is used when commencing treatment with this drug (refer to the TGA-approved Product Information treatment schedule) (ii) lanadelumab (iii) garadacimab
Treatment criteria:
Must be treated by a clinical immunologist or a specialist allergist

Administrative Advice: Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au. Applications for authorisation under this restriction should be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/hpos) Alternatively, applications for authority to prescribe can be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos Or mailed to: Services Australia Complex Drugs Reply Paid 9826 HOBART TAS 7001
Restriction Summary / Treatment of Concept
Category / Program: ☒ GENERAL - General Schedule (Code GE)
Prescriber type: ☒Medical Practitioners
Restriction type: ☒Authority Required (FULL assessment) in writing only via post/HPOS upload/Online Authorities)
Indication: Chronic treatment of hereditary angioedema Types 1 or 2
Treatment Phase: Initial 3: New patient (transitioning from PBS-subsidised lanadelumab or garadacimab)
Clinical criteria:
Patient must have been receiving lanadelumab or garadacimab through the PBS as routine prophylaxis for hereditary angioedema immediately prior to receiving this drug
AND
Clinical criteria:
The treatment must not be used in combination with any of: (i) C1-esterase inhibitor concentrate (ii) lanadelumab (iii) garadacimab
Treatment criteria:
Must be treated by a clinical immunologist or a specialist allergist
Administrative Advice: Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au. Applications for authorisation under this restriction should be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/hpos) Alternatively, applications for authority to prescribe can be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos Or mailed to: Services Australia Complex Drugs Reply Paid 9826 HOBART TAS 7001
Restriction Summary / Treatment of Concept
Category / Program: ☒ GENERAL - General Schedule (Code GE)
Prescriber type: ☒Medical Practitioners
Restriction type: ☒Authority Required (immediate assessment)
Indication: Chronic treatment of hereditary angioedema Types 1 or 2
Treatment Phase: Continuing preventative treatment

Clinical criteria:
Patient must have previously received PBS-subsidised treatment with this drug for this condition
AND
Clinical criteria:
Patient must have demonstrated or sustained an adequate response to PBS-subsidised treatment with this drug for this condition
AND
Clinical criteria:
The treatment must not be in combination with any of: (i) C1-esterase inhibitor concentrate (ii) lanadelumab (iii) garadacimab
Treatment criteria:
Must be treated by a specialist allergist or clinical immunologist, or in consultation with a specialist allergist or clinical immunologist
Prescribing instructions: Patients who have successfully transitioned to a lower dosing frequency should be reviewed every 6 months to ensure they continue to demonstrate a sustained response
Prescribing Instructions: At the time of the authority application, medical practitioners should request the appropriate number of repeats to provide for a continuing course of this drug sufficient for up to 24 weeks of therapy.
Prescribing Instructions: For the purposes of administering this restriction, an adequate response is a reduction of the baseline number of acute attacks of hereditary angioedema of a severity necessitating immediate medical intervention with either (i) icatibant, or (ii) C1-esterase inhibitor concentrate. The details of the reduction must be documented in the patient's medical records for auditing purposes
Administrative Advice: Applications for authorisation under this restriction may be made 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).

Flow on changes to lanadelumab and garadacimab

8.2 Update the following in PBS-subsidised **lanadelumab** (PBS item code: 12790E)

Amend the following clinical criterion with the addition of text in italics and deletions in strikethrough in all phases:

New	**Clinical criteria:**
	The treatment must not be used in combination with ~~either~~ *any of:* (i) C1-esterase inhibitor concentrate ~~or~~ (ii) garadacimab *(iii) donidalorsen*

Amend the following treatment phase and clinical criterion with the addition of text in italics under 'Treatment Phase: Initial 3: New patient (transitioning from PBS-subsidised garadacimab)'

	Treatment Phase: Initial 3: New patient (transitioning from PBS-subsidised garadacimab *or donidalorsen)*
	Clinical criteria:
	Patient must have been receiving garadacimab *or donidalorsen* through the PBS as routine prophylaxis for hereditary angioedema immediately prior to receiving this drug

8.3 Update the following for PBS-subsidised **garadacimab** (PBS item codes: 15317E, 15295B, 15305M, 15332Y)

Amend the following clinical criterion with the addition of text in italics and deletions in strikethrough in all phases:

	Clinical criteria:
	The treatment must not be used in combination with ~~either~~ *any of*: (i) C1-esterase inhibitor concentrate ~~or~~ (ii) lanadelumab *(iii) donidalorsen*

Amend the following treatment phase and clinical criterion with the addition of text in italics under 'Treatment Phase: Initial 3: New patient (transitioning from PBS-subsidised lanadelumab)'

	Treatment Phase: Initial 3: New patient (transitioning from PBS-subsidised lanadelumab *or donidalorsen*)
	Clinical criteria:
	Patient must have been receiving lanadelumab *or donidalorsen* through the PBS as routine prophylaxis for hereditary angioedema immediately prior to receiving this drug

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

Otsuka welcomes the PBAC recommendation to list donidalorsen for patients with hereditary angioedema (HAE) Types 1 and 2. HAE is a rare and unpredictable condition that can significantly impact patients' daily lives. We acknowledge the PBAC's consideration of the clinical evidence and the importance of providing people living with HAE access to a new treatment option. This recommendation provides clinicians and patients with an additional long-term prophylactic treatment choice, supporting more individualised care. We look forward to working with the Department to facilitate access to this important treatment as soon as possible.