6.04 VUTRISIRAN, Injection 25 mg (as sodium) in 0.5 mL pre-filled syringe, Amvuttra®, MEDISON PHARMA AUSTRALIA PTY LIMITED.

1 Purpose of submission

1.1 The submission requested Authority Required (written) listing of vutrisiran for the treatment of adult patients with wildtype or hereditary transthyretin amyloidosis with cardiomyopathy (ATTR-CM) with documented evidence of the transthyretin precursor protein present who have experienced at least one episode of hospitalisation that was a direct result of heart failure or have clinical evidence of heart failure without hospitalisation that required treatment with a diuretic for improvement.

1.2 Listing was requested on the basis of a cost-minimisation approach (CMA) versus tafamidis.

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

Component	Description
Population	Adults with ATTR-CM, with documented evidence of transthyretin precursor protein present and have all the following: • Experienced at least one episode of hospitalisation that was a direct result of heart failure or have clinical evidence of heart failure without hospitalisation that required treatment with a diuretic for improvement, • NYHA Class I or II, or NYHA Class III with NAC Stage 1 or 2 heart failure at the time of initiation • End-diastolic interventricular septal wall thickness of at least 12 mm on imaging • eGFR greater than or equal to 25 mL/minute/1.73 m^2
Intervention	Vutrisiran 25 mg SC injection Q3M.
Comparator	Tafamidis 61 mg tafamidis orally OD
Outcomes	Primary: • Composite endpoint of ACM and recurrent CV events (overall survival, CV-related mortality, CV-related hospitalisation) [a] Key Secondary: • Functional exercise capacity as measured by 6-MWT distance • HRQoL as measured by KCCQ-OS • ACM • Heart failure severity as measured by NYHA class changes • Adverse events from treatment
Clinical claim	In patients with ATTR-CM, vutrisiran 25 mg SC Q3M provides non-inferior effectiveness in terms of overall survival and cardiovascular-related mortality and hospitalisation [b], and non-inferior safety, when compared to treatment with tafamidis 61 mg oral tablet OD.

Source: Table 1-1, p15 of the submission

6-MWT = 6-minute walk test; ACM = all-cause mortality; ATTR-CM = transthyretin amyloid cardiomyopathy; CV = cardiovascular; eGFR = estimated glomerular filtration rate; HRQoL = health-related quality of life; KCCQ-OS = Kansas City Cardiomyopathy Questionnaire Overall Summary score; NAC = National Amyloidosis Centre; NYHA = New York Heart Association; SC = subcutaneous; OD = once daily; Q3M = once every 3 months.

[a] The submission's PICO table had a narrower definition of the composite endpoint ACM and recurrent CV events than HELIOS-B and throughout the submission. ACM included CV- and non-CV-related deaths, heart transplant, and left ventricular assistance device implant; and recurrent CV events included CV-hospitalisation, indeterminate hospitalisation, and urgent heart failure visit.
[b] The submission's PICO table based the clinical claim on a narrower definition of the composite outcome.

2 Background

Registration status

2.1 Vutrisiran was TGA registered for the ATTR-CM indication on 1 April 2026.

2.2 Vutrisiran was TGA registered on 21 June 2024 for the treatment of hereditary transthyretin amyloidosis (hATTR) in adult patients with stage 1 or 2 polyneuropathy (PN).

Previous PBAC consideration

2.3 The PBAC has previously considered tafamidis for ATTR-CM at the July 2020, March 2021, September 2021, and July 2023 meetings. At the July 2023 meeting, the PBAC recommended tafamidis for the treatment of patients with ATTR-CM with New York Heart Association (NYHA) class I-II heart failure. At its March 2026 meeting, the PBAC did not recommend the Sponsor's requested changes to the tafamidis risk sharing arrangement (RSA).[1]

2.4 At the November 2024 meeting, the PBAC recommended vutrisiran for the treatment of hATTR in adult patients with stage 1 or stage 2 PN on a CMA-basis against patisiran.

3 Requested listing

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

MEDICINAL PRODUCT medicinal product pack	Dispensed Price for Max. Qty	Max. qty packs	Max. qty units	№. of Rpts	Available brands
AMVUTTRA					
Vutrisiran 25 mg/0.5 mL injection, 1	$114,284.89 published price $32,053.66 effective price[a]	1	1	1	Amvuttra

[a] This was a placeholder effective price of vutrisiran

Category / Program: General Schedule
Prescriber type: ☒Medical Practitioners
Restriction type: ☒Authority Required (in writing only via post/HPOS upload)
Condition: Transthyretin amyloid cardiomyopathy
Indication: Transthyretin amyloid cardiomyopathy
Treatment Phase: First PBS-subsidised prescription for this drug
Clinical criteria:
The condition must have documented evidence of transthyretin precursor protein present
AND

[1] https://pbs.gov.au/industry/listing/elements/pbac-meetings/pbac-outcomes/2026-03/pbac-web-outcomes-03-2026-v3.pdf

Patient must have experienced at least one episode of hospitalisation that was a direct result of heart failure; OR Patient must have clinical evidence of heart failure without hospitalisation that required treatment with a diuretic for improvement
AND
Patient must have/have had New York Heart Association class I heart failure at the time of commencing this drug OR Patient must have/have had New York Heart Association class II heart failure at the time of commencing this drug OR Patient must have/have had New York Heart Association class III heart failure AND with National Amyloidosis Centre ATTR stage 1 or 2 disease at the time of commencing this drug
AND
Patient must have an end-diastolic interventricular septal wall thickness of at least 12 mm on imaging
AND
Patient must have an estimated glomerular filtration rate (eGFR) ~~greater than or equal to~~ *of at least* 25 mL/minute/1.73 m^2
AND
~~**Treatment criteria**~~ ***Population criteria:***
Patient must be at least 18 years of age.
~~**Treatment**~~ ***Clinical*** **criteria:**
The treatment must be the sole PBS-subsidised disease-modifying therapy for this condition
Treatment Phase: Second and subsequent PBS-subsidised prescriptions for this drug
Clinical criteria:
Patient must have previously received PBS-subsidised treatment with this drug for this condition
AND
Patient must have an estimated glomerular filtration rate (eGFR) ~~greater than or equal to~~ *of at least* 25 mL/minute/1.73 m^2
AND
The treatment must be ceased where the patient's heart failure has worsened to persistent New York Heart Association (NYHA) Class III with National Amyloidosis Centre (NAC) Stage 3, or to NYHA Class IV heart failure.
AND
The treatment must be ceased where the patient has received any of: (i) a heart transplant, (ii) a liver transplant, (iii) an implanted ventricular assist device
Treatment criteria:
The treatment must be the sole PBS-subsidised disease-modifying therapy for this condition
Prescribing Instructions: Patients with New York Heart Association class III heart failure must have *any of (i)* an ~~estimated glomerular filtration rate (~~eGFR~~)~~ ~~greater than or equal to~~ *of at least* 45 mL/minute/1.73 m^2 *(ii)* N-terminal pro–B-type natriuretic peptide (NT-proBNP) level ~~≤~~ *no more than* 3,000 ng/L to meet National Amyloidosis Centre ~~ATTR~~ stage 1 or 2 disease
Prescribing Instructions: *The authority application must be made via the Online PBS Authorities System (see www.servicesaustralia.gov.au/hpos) or in writing via HPOS form upload or mail and must include:* *(a) details of the proposed prescription; and* *(b) a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice).*
Prescribing Instructions: Evidence of clinical findings to establish the diagnosis: In this authority application, confirm that there is documented evidence of transthyretin precursor protein through either (1) alone, or, both (2) and (3), from the list below: Confirm the following has been completed: (1) amyloid expert centre histology findings derived via immunohistochemistry or mass spectrometry; OR (2) bone scintigraphy with grade 2-3 finding AND

(3) Confirm that there are negative results for monoclonal protein on each of the following three tests: (a) serum immunofixation (also known as protein electrophoresis) (b) urine immunofixation (c) serum free light chains blood test State which of (1) to (3) above has been completed, as well as the: (i) date of the finding, (ii) imaging/pathology report number/code that links the finding to the patient, (iii) name of the amyloid expert centre in this authority application (if applicable). For end-diastolic interventricular septal wall thickness (at least 12 mm), confirm that: (i) imaging (echocardiogram or magnetic resonance imaging) has been undertaken; and (ii) that the imaging report is stored in the patient's medical records. State the date that the imaging was performed and the thickness (in mm) in this authority application.	
Prescribing Instructions: Where this authority application is to transition a patient from non-PBS-subsidised to PBS-subsidised supply (i.e. a 'grandfathered' patient), confirm the following: (i) the patient's heart failure has not worsened to persistent New York Heart Association Class (NYHA) III with National Amyloidosis Centre (NAC) *stage 3* or NYHA Class IV heart failure while taking this drug.	
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	
Administrative Advice: The Australian Amyloid Network provides a list of clinic centres that manage amyloidosis. It also provides a list of Australian anatomical pathology laboratories to be contacted for tissue review and immunohistochemistry for amyloid typing. For the purposes of this restriction, these providers are considered to be amyloid expert centres.	
Concept ID (for internal Dept. use)	**Category / Program:** ☒ GENERAL - General Schedule (Code GE)
	Prescriber type: ☒Medical Practitioners
	Restriction type: ☒Authority Required (immediate assessment)
26040	**Indication:** Transthyretin amyloid cardiomyopathy
	Treatment Phase: Second and subsequent PBS-subsidised prescriptions for this drug
	Clinical criteria:
	Patient must have previously received PBS-subsidised treatment with this drug for this condition
	AND
20586	~~**Treatment criteria**~~ ***Clinical criteria:***
20585	The treatment must be the sole PBS-subsidised disease-modifying therapy for this condition
	AND
31649	**Clinical criteria:**

31648	Patient must have an estimated glomerular filtration rate (eGFR) ~~greater than or equal~~ *of at least* 25 mL/minute/1.73 m2
	AND
New	**Clinical criteria:**
New	The treatment must be ceased where the patient's heart failure has worsened to *any of* ~~persistent~~ *(i)* New York Heart Association (NYHA) Class III with National Amyloidosis Centre (NAC) stage 3 *(ii)* NYHA Class IV heart failure.
	AND
31658	**Clinical criteria:**
31657	The treatment must be ceased where the patient has received any of: (i) a heart transplant, (ii) a liver transplant, (iii) an implanted ventricular assist device
31651	**Treatment criteria:**
31650	Must be treated by a medical practitioner who is any of the following: (i) a cardiologist, (ii) a consultant physician with experience in the management of amyloid disorders; this authority application must be sought by the same medical practitioner providing treatment
32111	~~**Treatment criteria**~~ ***Prescribing Instructions:*** Confirm whether heart failure has worsened to NYHA Class III/IV since the last authority application (yes/no). If 'no', continued PBS subsidy is available. If 'yes', continued PBS subsidy is available, but the prescriber must undertake a review of the patient within 3 months to determine whether the worsening heart failure was transient or persistent. Where this subsequent clinical review finds that the heart failure persists as NYHA Class III/IV heart failure despite active treatment with this drug, then PBS subsidy is not available.
32088	**Prescribing Instructions:** If heart failure has worsened to NYHA Class III/IV since the last authority application, no ~~more than 2~~ repeat prescriptions must be prescribed.
New CAR	**Administrative Advice:** Applications for authorisation under this restriction may be made ~~in real time~~ using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).

3.2 The submission proposed a special pricing arrangement (SPA) for vutrisiran. However, as the effective price for tafamidis for ATTR-CM was not known to the Sponsor, a placeholder cost minimised effective price against the published prices of tafamidis for vutrisiran ($31,890.73 per syringe) was presented. The effective price for vutrisiran in hATTR-PN is [redacted] per syringe. Noting the low prevalence of hATTR-PN, the ESC considered that a small number of patients would be potentially eligible under both PBS items.

3.3 Compared to the current restrictions for tafamidis in ATTR-CM, patients classified as NYHA Class III with National Amyloidosis Centre (NAC) stage 1 or 2 were included in the requested restriction for vutrisiran, but these patients are not eligible for treatment under the current tafamidis restriction and tafamidis would not be the appropriate comparator for this subgroup (see para. 5.3). Patients classified as NYHA Class III with NAC stage 1 and 2 present with heart failure associated with marked functional limitations but have not yet developed advanced disease (amyloidosis) as indicated by the absence of both elevated N-terminal pro-brain natriuretic peptide (NT-proBNP; >3,000 ng/L) and renal dysfunction (estimated glomerular filtration rate

[eGFR] <45 mL/min/1.73m^2).[2] In a retrospective study of ATTR-CM patients between 2005 and 2022 that reported on NYHA class alongside NAC stage (N=2,042), NYHA Class III with NAC stage 1 or 2 contributed to 16% (304/1,903) of the ATTR-CM patients with non-missing data (Nitsche 2024).[3] Of the patients classified as NYHA Class III (n=461), 66% (304/461) were NAC 1 or 2. The ESC considered listing in patients with NYHA Class III with NAC Stage 1 or 2 to be inappropriate within the context of a CMA-based submission, as cost effectiveness in this population had not been established for the comparator of tafamidis.

3.4 The eGFR threshold at which treatment was permitted was lower in the requested restriction (based on the tafamidis restriction) compared to HELIOS-B (≥25 vs ≥30 mL/min/1.73 m^2), and the submission claimed that efficacy and safety was not expected to differ between the two eGFR thresholds. The evidence of efficacy and safety from vutrisiran in patients with more severe renal dysfunction was limited and was informed only by a post hoc analysis of HELIOS-B (Sheikh 2025).[4, 5] However, it was unclear if there were differences in efficacy or safety with vutrisiran in a patient with eGFR of 25-29 mL/min/1.73m^2 compared to a patient with eGFR ≥30 mL/min/1.73 m^2 (see para. 6.16).

3.5 Under the proposed restriction vutrisiran must be the sole PBS-subsidised disease-modifying therapy for ATTR-CM. In contrast, patients in HELIOS-B could receive tafamidis concomitantly (e.g., patients randomised to vutrisiran and were tafamidis-naïve could have initiated tafamidis during the trial; see para. 6.14). The current guidelines do not recommend concomitant use of tafamidis and vutrisiran.

3.6 Under the proposed restriction, patients are required to discontinue treatment following progression to persistent NYHA Class III with NAC stage 3 or NYHA Class IV, but this was inconsistent with HELIOS-B which allowed continued treatment despite progression to NYHA Class III with NAC stage 3 or NYHA Class IV. In HELIOS-B, 30.7% (100/326) and 31.6% (62/196) of patients from the overall and monotherapy populations, respectively, reported to have 'worsened from baseline NYHA class' after 30 months of vutrisiran treatment although the proportion who progressed to NYHA Class III with NAC stage 3 or NYHA Class IV was not reported.

---

[2] NAC stage 1 = NT-proBNP ≤3,000 ng/L AND eGFR ≥45 mL/min/1.73m^2; NAC stage 2 = NT-proBNP ≤3,000 ng/L OR eGFR ≥45 mL/min/1.73m^2; NAC stage 3 = NT-proBNP >3,000 ng/L AND eGFR <45 mL/min/1.73m^2.

[3] Nitsche C, et al. (2024). Expansion of the National Amyloidosis Centre staging system to detect early mortality in transthyretin cardiac amyloidosis. European Journal of Heart Failure. 26; 2008–2012 doi:10.1002/ejhf.3354

[4] Sheikh F, et al. (2025). Vutrisiran Improved Outcomes Versus Placebo in Patients with Transthyretin Amyloidosis with Cardiomyopathy and Severe Chronic Kidney Disease: Post Hoc Analysis of HELIOS-B. American Heart Association (AHA) Annual Scientific Sessions 2025. November 7-10 2025. https://capella.alnylam.com/wp-content/uploads/2025/11/VUTRIS1.pdf

[5] Sheikh F, et al. (2025). Abstract 4362795: Vutrisiran Improved Outcomes Versus Placebo in Patients with Transthyretin Amyloidosis with Cardiomyopathy and Severe Chronic Kidney Disease: Post Hoc Analysis of HELIOS-B. Circulation. 152 (3). https://doi.org/10.1161/circ.152.suppl_3.4362795

3.7 The submission requested grandfathering criteria for patients who commence treatment with vutrisiran prior to it being PBS listed and who meet the PBS criteria. The submission noted that vutrisiran will be made available via a compassionate access program.

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

4 Population and disease

4.1 Transthyretin amyloidosis (ATTR) is a progressive, systemic disorder caused by the extracellular deposition of misfolded transthyretin (TTR) amyloid fibrils in multiple organs and tissues. ATTR can be inherited as an autosomal dominant variant of the *TTR* gene (hATTR) or caused by the deposition of wildtype transthyretin protein (ATTRwt).

4.2 There are two predominant phenotypes of ATTR: ATTR-CM and ATTR-PN. ATTR-CM is characterised by TTR amyloid fibril deposition in the cardiac atrial and ventricular walls. Over time this leads to myocardial hypertrophy and progressive restrictive cardiomyopathy (CM) which deteriorates cardiac function over time contributing to heart failure, cardiac conduction disorders (e.g. atrial fibrillation), and premature death (Tschöpe 2025).[6] ATTR-PN results from the deposition of TTR amyloid fibrils in the nerves, causing sensory neuropathy, motor dysfunction, and autonomic dysfunction. Patients can present with predominantly CM, predominantly PN, or mixed CM/PN phenotype.

4.3 ATTR-CM is most prevalent in ATTRwt, while phenotypes can vary in hATTR patients depending on the *TTR* variant (e.g., *Val122Ile* [*V122I*] variant is associated with the predominantly CM phenotype). In a retrospective analysis of the THAOS registry data (N=4,428), among the ATTR patients, 31.9% (1,413/4,428) had the CM phenotype, 38.7% (1,712/4,428) had the PN phenotype, and 24.5% (1,085/4,428) had the mixed CM/PN phenotype and according to genotype, ATTRwt patients had the CM phenotype (76.1% [1,073/1,410]) and mixed phenotype (23.9% [337/1,410]), while in hATTR patients, 56.7% (1,711/3,017) had the PN phenotype, 11.3% (340/3,017) had CM phenotype, and 24.8% (748/3,017) had mixed phenotype (Gentile 2023).[7]

4.4 Heart failure is the most common cardiovascular (CV) manifestation in ATTR-CM. Based on patients with symptomatic ATTR-CM from the Transthyretin Amyloidosis Outcomes Survey (THAOS) registry, heart failure was reported in 87% (1,227/1,410) and 72% (787/1,088) in ATTRwt and hATTR patients respectively (Gentile 2023).

[6] Tschöpe C, et al. (2025). Transthyretin Amyloid Cardiomyopathy-2025 Update: Current Diagnostic Approaches and Emerging Therapeutic Options. J Clin Med. 2025 Jul 7;14(13):4785. doi: 10.3390/jcm14134785. PMID: 40649158; PMCID: PMC12250813.

[7] Gentile L, et al. (2023). A 15-year consolidated overview of data in over 6000 patients from the Transthyretin Amyloidosis Outcomes Survey (THAOS). Orphanet J Rare Dis 18, 350 (2023). https://doi.org/10.1186/s13023-023-02962-5

Patients were more commonly classified as NYHA Class I or II (71.4% [855/1,197] in wildtype; 42.0% [503/781] in hereditary) compared to NYHA Class III (26.3% [315/1,197] in wildtype; 31.5% [246/781] in hereditary). Common manifestations alongside CV involvement include carpal tunnel syndrome (i.e., nerve compression at the wrist), spinal canal stenosis (i.e., narrowing of the spinal canal), and ruptured bicep tendon. While the kidneys are not commonly directly involved in ATTR-CM, cardiac dysfunction may have secondary impacts on kidney function (Bart 2024; Kittleson 2025).[8, 9]

4.5 ATTR-CM disproportionately impacts males (≥80%) and disease onset typically occurs after 60 years of age. Onset can occur earlier in hATTR patients dependent on the *TTR* variant. In an Australian and New Zealand ATTR-CM cohort in 2022 (N=515), most patients were male (88% [455/515]), and the mean age was from 62 (hATTR) to 78 years (ATTRwt).[10]

4.6 Median survival from diagnosis for untreated patients with ATTR-CM ranges between 2.1 and 5.8 years. Older age, CV involvement (e.g., heart failure, atrial fibrillation), and renal dysfunction have been identified as prognostic risk factors for mortality (Guijarro 2025, Muller 2024, Gilmore 2018, Ioannou 2025). [11, 12, 13, 14]

4.7 Diagnosis of ATTR-CM is confirmed either by tissue biopsy with amyloid deposits confirmed by Congo Red staining; or bone scintigraphy with grade 2-3 finding and confirmation of negative results for monoclonal protein on all three of the following tests: serum immunofixation, urine immunofixation, and serum free light chains blood test (i.e., to rule out amyloid light chain amyloidosis). These diagnostic criteria are included under the current tafamidis restriction. The PBAC previously noted input from the Australian Amyloidosis Network (AAN) that there is "consensus that ATTR-CM can be accurately diagnosed without the need for cardiac biopsy by the use of bone scintigraphy" (para. 6.4, tafamidis Public Summary Document [PSD], July 2023 PBAC Meeting).

---

[8] Bart NK, et al. (2024). 2024 Australia-New Zealand Expert Consensus Statement on Cardiac Amyloidosis. Heart Lung Circ;33(4):420-442. doi: 10.1016/j.hlc.2023.11.027. PMID: 38570258.

[9] Kittleson, M. et al. (2025). Transthyretin Cardiac Amyloidosis Evaluation and Management: 2025 ACC Concise Clinical Guidance. JACC. 87 (5) 549–565. https://doi.org/10.1016/j.jacc.2025.09.004

[10] Geenty P, et al. (2025). Cardiac Subcommittee of the Australian Amyloidosis Network. Transthyretin Cardiac Amyloidosis in Australia and New Zealand-A Multi-Site Snapshot for 2022. Heart Lung Circ.;34(1):48-57. doi: 10.1016/j.hlc.2024.05.014. PMID: 39592278.

[11] Guijarro D, et al. (2025). Characteristics and Prognosis of Wild-Type Transthyretin Amyloid Cardiomyopathy Patients Diagnosed Before 65 Years Old. JACC Adv. 4 (12_Part_2). https://doi.org/10.1016/j.jacadv.2025.102354

[12] Muller ML, et al. (2024). Outcomes in Cardiac Transthyretin Amyloidosis and Association With New York Heart Association Class: Real-World Data. Journal of the American Heart Association. Volume 13. No.14. https://doi.org/10.1161/JAHA.123.033478

[13] Gillmore JD, et al. (2018). A new staging system for cardiac transthyretin amyloidosis. Eur Heart J. 2018 Aug 7;39(30):2799-2806. doi: 10.1093/eurheartj/ehx589. PMID: 29048471.

[14] Ioannou A, et al. (2025) Kidney Outcomes in Transthyretin Amyloid Cardiomyopathy. JAMA Cardiol. 10(1), 50–58. doi:10.1001/jamacardio.2024.4578

4.8 Prevalence estimates of ATTR-CM in Australia are uncertain, and it was acknowledged that reliable Australian-based epidemiological studies were lacking. The submission presented a Clinician Survey Report of Australian clinicians with experience in diagnosing and or managing patients with ATTR-CM (n=30, 10 December 2025 to 27 January 2026). In this report the estimated median prevalent population was 9,500 (interquartile range [IQR] 3,500, 15,000; n=16) and the submission estimated this corresponded to a prevalence of 435 per million. International estimates of prevalence rates provided by the submission ranged from 33 to 224 per million. The PBAC had previously expressed that "ATTR-CM is likely currently significantly underdiagnosed, but this is difficult to quantify due to the nature of the data sources available" (para. 7.16, tafamidis PSD, July 2020 PBAC meeting). The requested ATTR-CM (wildtype or hereditary) population was larger than the current PBS-listed population for vutrisiran in ATTR-PN (hereditary). For comparison, in the PBAC's consideration of hATTR-PN, a prevalence of 7.52 per million was used which the PBAC generally considered was reasonable for estimating the size of the treated population, as the Australian hATTR population is small and well-defined (Table 14 and para. 7.11, vutrisiran [hATTR-PN] PSD, November 2024 PBAC meeting).

4.9 Vutrisiran is a chemically stabilised double-stranded small interfering ribonucleic acid (siRNA) that specifically targets variant and wildtype TTR messenger RNA (mRNA) and is covalently linked to a ligand containing three Nacetylgalactosamine (GalNAc) residues to enable delivery of the siRNA to hepatocytes. Through a natural process called RNA interference (RNAi), vutrisiran causes the catalytic degradation of TTR mRNA in the liver, resulting in the reduction of variant and wild-type serum TTR protein levels.

4.10 Vutrisiran (25 mg/0.5 mL pre-filled syringe) is administered subcutaneously (SC) once every three months (Q3M). The submission proposed that vutrisiran can be administered via healthcare professional or trained caregiver or patient. The submission recommended vitamin A supplementation at a dose of 2500 IU daily.

4.11 The submission positioned vutrisiran as a direct substitute to tafamidis as a first-line treatment in wildtype or hereditary ATTR-CM in combination with supportive care.

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

5 Comparator

5.1 The submission nominated tafamidis as the main comparator as it is the only TGA-approved and PBS-listed disease-modifying treatment for ATTR-CM. Tafamidis is a TTR stabiliser that acts by binding to the thyroxine-binding site on TTR, thereby stabilising TTR and slowing the dissociation of TTR tetramers into monomers.

5.2 The recommended dose of tafamidis was 61 mg orally once daily (OD). Tafamidis 61 mg was considered bioequivalent to tafamidis 80 mg formulation (tafamidis PI), which was used in the ATTR-ACT trial.

5.3 The current PBS restriction for tafamidis is limited to patients with NYHA Class I or II and is narrower than the requested restriction for vutrisiran which additionally included patients with NYHA Class III with NAC stage 1 or 2 (~16% of ATTR-CM met these criteria; see para. 3.3). The PBAC previously considered that the magnitude of benefit from tafamidis was uncertain in patients with NYHA Class III from ATTR-ACT. The PBAC previously noted that NYHA class may be a treatment effect modifier, with tafamidis treatment being associated with an increase in hospitalisations and an uncertain impact on survival in patients with NYHA Class III disease based on subgroup data (para. 7.9, tafamidis PSD, July 2020 PBAC Meeting).

5.4 Tafamidis was only an appropriate comparator for the NYHA Class I or II subgroup but not the NYHA Class III with NAC stage 1 or 2 subgroup, whereby best supportive care (BSC) may be a more appropriate comparator. This was not considered by the submission. BSC might include supportive cardiac-related therapies (e.g., oral loop diuretics or sodium-glucose cotransporter-2 [SGLT-2] inhibitors), non-specific TTR therapies or fibril disruptors (e.g., green tea extract, diflunisal, or doxycycline).

5.5 The ESC agreed with the evaluation that BSC was the more appropriate comparator for the NYHA Class III subgroup as the PBAC had previously considered tafamidis to have uncertain effectiveness in the Class III population (Tafamidis, PSD, July 2020 and March 2021 PBAC Meetings).

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

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer inputs

6.2 The PBAC noted and welcomed the input from individuals (3), one medical organisation (the Australian Amyloidosis Network (AAN) cardiac subcommittee) and one consumer organisation (Cardiomyopathy Australia New Zealand) via the Office of Health Technology Assessment Consultation Hub. The inputs from individuals described the importance of additional treatment options for ATTR-CM as tafamidis is not fully effective for every patient and discussed the impacts of ATTR-CM on daily life including fatigue and shortness of breath that substantially restrict lifestyle and the ability to contribute to activities at home and in the community. The input also described vutrisiran as effective, safe and easy to use, with the potential to slow disease progression, prolong life and preserve quality of life.

6.3 The PBAC noted the advice from the AAN cardiac subcommittee stated vutrisiran is expected to provide similar or improved effectiveness compared to tafamidis for ATTR-CM and that it is a particularly important treatment option for patients who do not adequately respond to or do not tolerate tafamidis, with a convenient

administration schedule that is well accepted by patients.

6.4 The PBAC also noted the input from Cardiomyopathy Australia New Zealand supporting the listing of vutrisiran. The input outlined that different treatment approaches suit different patients, and that from patient perspective, preserving functional capacity, reducing hospitalisations, maintaining independence and slowing disease progression are highly important outcomes, and stated vutrisiran is an important treatment option for some patients to achieve these outcomes.

Clinical trials

6.5 No head-to-head trials were identified that compared vutrisiran and tafamidis in ATTR-CM. The submission identified two randomised trials of vutrisiran and tafamidis, respectively:

- HELIOS-B (N=654) compared vutrisiran 25 mg Q3M (n=326) to placebo (n=328) in adult patients with ATTR-CM.
- ATTR-ACT (N=441) compared tafamidis meglumine 80 mg (n=176) and tafamidis meglumine 20 mg (n=88) to placebo (n=177) in adult patients with ATTR-CM.

6.6 The submission considered it was not feasible to conduct a reliable indirect treatment comparison (ITC) of vutrisiran from HELIOS-B and tafamidis from ATTR-ACT due to differences in baseline patient characteristics and background care, noting that ATTR-ACT was an older trial (see para. 6.18). Instead, the submission informed the clinical claim of efficacy based on a *post hoc* analysis of HELIOS-B that compared the 'vutrisiran monotherapy group' (i.e., patients randomised to vutrisiran who had no prior tafamidis use at baseline) and the 'tafamidis monotherapy group' (i.e., patients randomised to placebo who had tafamidis use at baseline) using the stabilised inverse probability of treatment weighting (IPTW) methodology. A naïve unanchored comparison of efficacy from HELIOS-B and ATTR-ACT was presented as supplementary evidence.

6.7 The submission's safety clinical claim was informed by a naïve side by side comparison of the vutrisiran monotherapy group with the tafamidis monotherapy group from HELIOS-B as well as with the tafamidis treatment arm in ATTR-ACT.

6.8 The submission noted that a matching adjusted indirect comparison (MAIC) between HELIOS-B and ATTR-ACT was presented in the vutrisiran submission to the NICE[15]. The Pre-Sub-Committee Response PSCR considered the MAIC to be a lower level of evidence compared to the stabilised IPTW approach presented in the submission.

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

[15] NICE. (2025). "National Institute for Health and Care Excellence. Vutrisiran for treating transthyretin related amyloidosis with cardiomyopathy (TA1115)." available at https://www.nice.org.uk/guidance/ta1115.

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
HELIOS-B (NCT04153149)	A Phase 3, Randomized, Double-blind, Placebo-controlled, Multicentre Study to Evaluate the Efficacy and Safety of Vutrisiran in Patients with Transthyretin Amyloidosis with Cardiomyopathy (ATTR Amyloidosis with Cardiomyopathy)	Clinical Study Report May 2024
	Fontana M, et al. Vutrisiran in Patients with Transthyretin Amyloidosis with Cardiomyopathy	NEJM 2025;392(1):33-44.
	Witteles R, et al. Vutrisiran Improves Survival and Reduces Cardiovascular Events in ATTR Amyloid Cardiomyopathy: HELIOS-B.	JACC 2025; 85(20): 1959-1970
	Witteles R, et al. Outcomes of the HELIOS-B Monotherapy Population: A Post Hoc Analysis Censoring Data Following Tafamidis Initiation.	Annual Scientific Meeting of the Heart Failure Society of America. September 26-29, 2025.
	Fontana M, et al. Primary Results from HELIOS-B, a Phase 3 Study of Vutrisiran in Patients with Transthyretin Amyloidosis with Cardiomyopathy.	European Society of Cardiology Congress 30 August – 2 September 2024
	Sheikh F, et al. Vutrisiran Improved Outcomes Versus Placebo in Patients with Transthyretin Amyloidosis with Cardiomyopathy and Severe Chronic Kidney Disease: Post Hoc Analysis of HELIOS-B.	American Heart Association (AHA) Scientific Sessions, November 7–10, 2025.
	Garcia-Pavia P, et al. HELIOS-B: 12-Month Results from the Open-Label Extension Period of Vutrisiran in Patients with Transthyretin Amyloidosis with Cardiomyopathy.	ESC Congress 2025 with World Congress of Cardiology 31 August 2025
	Witteles R, et al. Vutrisiran Reduces All-Cause Mortality, Cardiovascular Mortality and Cardiovascular Events in Patients with Transthyretin Amyloid Cardiomyopathy: Analysis from the HELIOS-B Trial.	Heart Failure 17–20 May 2025
ATTR-ACT (NCT01994889)	A multicentre, international, phase 3, double blind, placebo-controlled, randomised study to evaluate the efficacy, safety, and tolerability of daily oral dosing of tafamidis meglumine (PF-06291826) 20 mg or 80 mg in comparison to placebo in subjects diagnosed with transthyretin cardiomyopathy (TTR-CM)	August 2018
	Maurer S, et al. Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy.	NEJM 2018;379(11):1007-1016.
	Damy T, et al. Efficacy and safety of tafamidis doses in the tafamidis in transthyretin cardiomyopathy clinical trial (ATTR-ACT) and long-term extension study.	Eur J Heart Fail 2021; 23(2): 277–285.

Source: Table 2-5, pp48-9 of the submission

6.10 The key features of the randomised trials are summarised in Table 3.

Table 3: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Analysis
Vutrisiran vs placebo						
HELIOS-B primary analysis	Overall population VUT 25 mg (N=326) PBO (N=328) Monotherapy population VUT 25 mg (n=196) PBO (n=199)	P3, R, DB, MC 36 mths + 12 mths OLE	*Low*	18-85 years, ATTR-CM, NYHA I, II, or III with NAC 1 or 2, CV involvement[c]	Composite (ACM + recurrent CV events [d]), ACM, recurrent CV events, 6-MWT, KCCQ-OS, NYHA	Naïve efficacy and safety comparison
Tafamidis vs placebo						
ATTR-ACT	TAF 20 mg (N=88) TAF 80 mg (N=176) PBO (N=177)	P3, R, DB, MC 30 mths	Unclear	18-90 years, ATTR-CM, NYHA I-III, CV involvement[c]	Composite (ACM + CV hospitalisation) ACM, CV mortality, CV hospitalisation, 6MWT, KCCQ-OS, EQ-5D-3L	Naïve efficacy and safety comparison
Vutrisiran vs tafamidis						
HELIOS-B *post hoc* analysis	VUT 25 mg monotherapy[a] (n=196) TAF monotherapy[b] (n=129)	Stabilised IPTW 36 mths	*High*	18-85 years, ATTR-CM, NYHA I, II, or III with NAC 1 or 2, CV involvement[c]	Composite (ACM + recurrent CV events)	Efficacy clinical claim

Source: Section 2.2 and Section 2.3 of the submission; Table 4, tafamidis PSD, July 2023 PBAC Meeting

ACM = all-cause mortality; CM = cardiomyopathy; CV = cardiovascular; DB = double blind; IPTW = inverse probability of treatment weighting; KCCQ-OS = Kansas City Cardiomyopathy Questionnaire Overall Summary Score; MC = multi-centre; mths = months; N = number of patients; NAC = National Amyloidosis Centre; NYHA = New York Heart Association; OLE = open label extension; PBO = placebo; P3 = phase 3 trial; R = randomised; TAF = tafamidis; VUT = vutrisiran; 6-MWT = 6-minute walk test;

[a] Vutrisiran monotherapy group were patients randomised to vutrisiran and had no tafamidis use at baseline

[b] Tafamidis monotherapy group were patients randomised to placebo and had tafamidis use at baseline. Tafamidis dose was the recommended dose in the patient's local jurisdictions' which was not explicitly reported.

[c] Evidence of cardiac involvement by echocardiography with an end-diastolic interventricular septal wall thickness ≥ 12 mm.

[d] Recurrent CV events defined as any CV hospitalisation, indeterminate hospitalisation, and urgent heart failure visit

Notes:

Blue shaded cells indicate evidence previously considered by the PBAC

6.11 The post hoc stabilised IPTW analysis was considered at a high risk of bias as the comparison of vutrisiran monotherapy and tafamidis monotherapy was a non-randomised cross arm comparison in which known and unknown confounders may no longer be balanced. Comparing patients with and without tafamidis use at baseline raises the concern that patients were fundamentally different at baseline. For example, patients with baseline tafamidis use may have more severe disease compared to patients without tafamidis use at baseline, which may favour vutrisiran in the post hoc comparison. The ESC noted that the PSCR provided additional information from the analysis including baseline characteristics of vutrisiran monotherapy and tafamidis monotherapy groups before and after stabilised IPTW.

6.12 Baseline characteristics (pre-IPTW adjustment) indicated that the tafamidis monotherapy group had a higher proportion of patients with NYHA Class III with NAC stage 1 or 2 (13.2% [17/129] vs 4.6% [9/196]), and a longer duration of disease (median 1.53 vs 0.50 years) compared to the vutrisiran monotherapy group. Notably, patients with NYHA Class III with NAC stage 1 or 2 would not be eligible for PBS subsidised tafamidis in clinical practice, and it was unclear if these patients in the tafamidis monotherapy group were excluded from the stabilised IPTW analysis. The

PBAC had previously considered that the magnitude of benefit from tafamidis was uncertain in patients with NYHA Class III from ATTR-ACT, as such, including these patients potentially biased the comparison against tafamidis (see para. 5.3).

6.13 Treatment details relating to the tafamidis use (e.g., dose, frequency, compliance, or duration) were not reported in the tafamidis monotherapy group from HELIOS-B. As such, it was unclear whether tafamidis use in the stabilised IPTW was generalisable to clinical practice in Australia.

6.14 Drop-in concomitant tafamidis use (i.e. initiation of tafamidis during the trial duration of HELIOS-B) was reported in 44/196 (22.5%) patients in vutrisiran monotherapy group. Concomitant use would be not permitted under the requested restriction for vutrisiran (see para. 3.5) and was not accounted for in the primary or post hoc stabilised IPTW analysis. As such, there was potential confounding and reduced applicability of the vutrisiran treatment effect due to tafamidis drop-in. A separate post hoc analysis that censored patients with tafamidis drop-in was conducted in Witteles 2025, but this did not adequately address the potential incremental benefit from tafamidis since the benefit from vutrisiran in these patients was also censored, thus did not entirely mitigate this uncertainty.[16, 17]

6.15 Concomitant SGLT-2 inhibitors use for the treatment of heart failure was reported at baseline in 3.1% (10/326) and 3.4% (11/328) of patients in the vutrisiran and placebo arms respectively. During HELIOS-B, SGLT-2 inhibitor use in the overall population was reported to be 29.1% (91/326) and 30.5% (100/328) in the vutrisiran and placebo arms respectively. There is evidence of improved all-cause mortality (ACM) and CV mortality in ATTR-CM patients receiving SGLT-2 inhibitors compared to those who were not (Khan 2026).[18] At the May 2025 and September 2025 meeting, the PBAC recommended the expansion of the use of empagliflozin and dapagliflozin for the treatment of chronic kidney disease (CKD), depending on eGFR and urinary albumin to creatinine ratio (para. 1.2, 5.1 and 5.3, dapagliflozin PSD, September 2025 PBAC meeting). As such, the population with ATTR-CM who may be using SGLT-2 inhibitors in the proposed PBS population may be substantially higher than in HELIOS-B, given CKD is commonly presented with progressive CM. However, potential treatment effect interactions between vutrisiran and SGLT-2 inhibitors in ATTR-CM remained unclear since no analysis was presented that assessed the impact of drop-in SGLT-2 inhibitor use and no subgroup analysis of baseline SGLT-2 inhibitor use was conducted in HELIOS-B (but acknowledged that patient numbers at baseline were small). The PSCR stated that SGLT-2 inhibitors were considered part of standard-of-care

[16] Witteles R, et al. (2025). Outcomes of the HELIOS-B monotherapy population: A post hoc analysis censoring data following tafamidis initiation, Archives of Cardiovascular Diseases, Volume 119, Issue 1, Pages S38-S39, https://doi.org/10.1016/j.acvd.2025.10.069.

[17] https://www.rnaiscience.com/sites/default/files/2025-09/Witteles_HFSA2025_H-B-monotherapy_D3_oral_22Sept2025_v3.pdf

[18] Khan A., et al. (2026). Role SGLT2 inhibitor therapy in patients with transthyretin cardiac amyloidosis: a GRADE assessed systematic review and meta-analysis. *Acta Cardiologica*, *81*(2), 164–172.

background therapy and that available evidence was not suggestive of attenuation of vutrisiran efficacy in patients receiving contemporary heart failure therapies. The ESC maintained that background SGLT-2 inhibitors in the HELIOS-B trial remained low compared to the Australian population, therefore the potential extent of benefit with vutrisiran may be reduced in the Australian context, albeit to an uncertain degree.

6.16 Sheikh 2025 assessed the efficacy and safety of vutrisiran in patients who advanced to stage 4 CKD or greater (eGFR <30 mL/min/1.73 m^2) in HELIOS-B *post hoc* and was relied upon by the submission to support expanding eGFR threshold criterion in the requested restriction (see para. 3.4). In this subgroup, the composite HR for vutrisiran compared to placebo was reported as 0.47 (95% CI 0.26, 0.85) in the overall population (n=63) and 0.53 (95% CI 0.25, 1.13) in the monotherapy population (n=37). The results of this analysis should be interpreted with caution since the 95% CIs were wide and also included one in the monotherapy population which may suggest that the patient numbers were insufficient for informing the comparative efficacy in this subgroup; and it was not clear at what point and how long patients were classified as having stage 4 CKD from a baseline mean eGFR >45 mL/min/1.73 m^2.

6.17 The PBAC has previously considered the risk of bias of ATTR-ACT to be unclear (para. 6.8 to 6.10, tafamidis PSD, July 2023 PBAC Meeting).

6.18 Differences in baseline characteristics potentially suggested patients in HELIOS-B had less severe disease compared to patients in ATTR-ACT (e.g., lower proportion of patients with NYHA Class III (9.5% [62/654] vs 32.0% [141/441]), NAC stage 3 (4.6% [30/654] vs 19.8% [70/353][19]), and lower median NT-proBNP levels [1,801-2,021 vs 2,995-3,161 pg/mL] compared to ATTR-ACT).

Comparative effectiveness

IPTW analysis comparing monotherapy subgroups from HELIOS-B

6.19 The results from the *post hoc* stabilised IPTW analysis that compared the vutrisiran monotherapy group to the tafamidis monotherapy group from HELIOS-B over the 36-month double-blind period is presented in Table 4.

[19] NAC stage was only reported in tafamidis 80 mg arm. Denominator was tafamidis 80 mg (n=176) + placebo (N=177).

Table 4: *Post hoc* stabilised IPTW analysis of vutrisiran monotherapy compared to tafamidis monotherapy from HELIOS-B

	Vutrisiran monotherapy (N=196) vs tafamidis monotherapy (N=129)
Composite HR (95% CI) at 36 months	0.83 (0.54, 1.29)
ACM HR (95% CI) at 42 months	0.81 (0.50, 1.34)
Recurrent CV events RR (95% CI) at 36 months	0.82 (0.62, 1.08)

Source: Table 2-37, p111 of the submission

ACM = all-cause mortality; CI = confidence interval; CV = cardiovascular; HR = hazard ratio; IPTW = inverse probability of treatment weighting.

Notes:

HR < 1 favours vutrisiran

6.20 From the stabilised IPTW comparison of vutrisiran monotherapy and tafamidis monotherapy, the hazard ratio (HR) for composite outcome of ACM and recurrent CV events at 36 months (HR = 0.83, 95% CI 0.54, 1.29), ACM at 42 months (HR = 0.81, 95% CI 0.50, 1.34) and recurrent CV events at 36 months (HR = 0.82, 95% CI 0.62, 1.08) had 95% CIs which included one. The submission claimed there was a 'numerical relative reduction' compared to tafamidis.

6.21 A non-inferiority margin was not proposed. The 95% CIs derived from the stabilised IPTW analysis were wide and suggested that vutrisiran may have a 29% higher risk of experiencing ACM or a recurrent CV event (composite), a 34% higher risk of ACM, and an 8% higher risk of a recurrent CV event compared to tafamidis. A non-inferiority margin of 1.1 for the upper 95% CI was noted but not applied in the submission. The PSCR acknowledged the width of the confidence intervals, however, argued the non-inferiority margin was not formally proposed and this reflected limitations associated with sample size as opposed to evidence of reduced treatment effect. While the ESC accepted the PSCR's claim that the non-inferiority margin did not form part of the sponsor's main argument, the ESC noted that if this margin was applied, then non-inferiority of the primary composite endpoint and ACM would not be met (i.e., the upper 95% CI of 1.29 and 1.34 exceeded 1.1), and would not support non-inferiority.

6.22 The evaluation and ESC considered the results from the stabilised IPTW analysis were considered highly uncertain as it was a non-randomised comparison conducted *post hoc* that may not have sufficient statistical power to determine non-inferiority. In addition, treatment utilisation in the vutrisiran and tafamidis monotherapy groups had uncertain applicability to clinical practice (see para. 6.12 to 6.15).

HELIOS-B

6.23 Tafamidis was not the appropriate comparator for patients classified as NYHA Class III with NAC stage 1 or 2 (see para. 5.3) and as such the stabilised IPTW analysis was not applicable to informing the comparative effectiveness of vutrisiran for this subgroup. The comparative efficacy of vutrisiran vs placebo in patients with NYHA Class III with NAC stage 1 or 2 was informed by subgroup data from HELIOS-B and is presented in Table 5 alongside the complement subgroup (NYHA Class I or II), and the overall and monotherapy populations. Importantly, the NYHA Class III with NAC stage 1 or 2 subgroup result was informed by low patient numbers (n=62 in overall population and n=27 in the monotherapy population).

Table 5: Composite endpoint (ACM + CV events) in the overall and monotherapy populations including the NYHA Class I or II and NYHA Class III + NAC stage 1 or 2 subgroups over the 36-month DB period from HELIOS-B

Composite endpoint (ACM + CV)	Overall			Monotherapy		
	Total overall (N=654)	NYHA I or II (n=592)	NYHA III + NAC 1/2 (n=62)	Total monotherapy (N=395)	NYHA I or II (n=368)	NYHA III + NAC 1/2 (n=27)
HR (95% CI); p-value[a, b]	**0.72 (0.56, 0.93); 0.0118**	0.73 (0.55, 0.96)	0.68 (0.33, 1.41)	**0.67 (0.49, 0.93); 0.0162**	0.73 (0.53, 1.02)	0.31 (0.09, 1.02)

Source: Table 2-19, p77 and Table 2-39, p113; Figure 2-7, p78 of the submission

ACM = all-cause mortality; CI = confidence interval; CV = cardiovascular; DB=double-blind; HR = hazard ratio; NT-proBNP = N-terminal prohormone B type natriuretic peptide; N or n = patient numbers; NR = not reported; NYHA = New York Heart Association.

[a] Composite endpoint analysed using modified Andersen-Gill model including treatment group, log-transformed NT-proBNP, type of ATTR amyloidosis, NYHA class, and age group as covariates. In the overall population, the model was stratified by baseline tafamidis use.

[b] p-values reported for NYHA class subgroups

Notes:

Bold text indicates statistical significance as per the prespecified statistical testing protocol

6.24 In the primary analysis of HELIOS-B, vutrisiran demonstrated a statistically significant reduction in the risk of the composite outcome of ACM or recurrent CV events compared to placebo which was observed over 36 months in the overall population (HR = 0.72, 95% CI 0.56, 0.93; p=0.0118) and monotherapy population (HR = 0.67, 95% CI 0.49, 0.93; p=0.0162).

6.25 The treatment effect appears to have been maintained at 42 and 48 months in the overall (HR = 0.69, 95% CI NR; HR = 0.66, 95% CI 0.51, 0.85, respectively) and monotherapy populations (HR = 0.64, 95% CI NR; HR = 0.60, 95% CI 0.43, 0.84, respectively).

6.26 The treatment benefit of vutrisiran compared to placebo in NYHA Class III with NAC stage 1 or 2 patients was uncertain, as while the point estimate HR favoured vutrisiran, the upper bound of the 95% CI exceeded one (composite outcome HR = 0.68, 95% CI 0.33, 1.41; n=62 in overall population; HR = 0.31, 95% CI 0.09, 1.02; n=27 in monotherapy population). The wide 95% CIs in these comparisons may have indicated that the sample sizes were not sufficient to inform comparative effectiveness in this population. The ESC noted the 95% confidence intervals were wide for this group, reflecting the small sample size for the overall and monotherapy populations.

6.27 Component analysis indicated nominally significant reductions in the risk of ACM (HR = 0.69, 95% CI 0.49, 0.98; p=0.0389) and recurrent CV events (relative risk [RR] = 0.73, 95% CI 0.61, 0.88; p=0.001) at 36 months in the overall population. ACM in the overall population did not meet the multiplicity significance p-value (0.0389 > 0.025), while recurrent CV events were not included in multiplicity testing.

6.28 In the monotherapy population, there was a nominally significant difference in recurrent CV events (RR = 0.68, 95% CI 0.53, 0.86; p=0.0012) but no significant difference in ACM (HR = 0.71, 95% CI 0.47, 1.06; p=0.1179) at 36 months. ACM in the monotherapy population 95% CIs included one, and recurrent CV events were not included in multiplicity testing.

ATTR-ACT

6.29 In ATTR-ACT, the Finkelstein-Schoenfeld prioritised pairwise comparison of ACM and CV hospitalisation suggested a statistically significant difference between the pooled

tafamidis group versus placebo in at least one or both outcomes (p=0.006). A significant difference was observed for individual outcomes of ACM (HR = 0.70, 95% CI 0.51, 0.96) and CV-related hospitalisations (RR = 0.68, 95% CI 0.56, 0.81) at 30 months.

Naïve unanchored comparison between HELIOS-B and ATTR-ACT

6.30 A naïve unanchored comparison between HELIOS-B and ATTR-ACT was presented in the submission, however the evaluation considered it was unclear how the naïve comparison of HELIOS-B and ATTR-ACT could be interpreted to support a claim of non-inferiority, as there were differences in patient characteristics (see para. 6.18), the measurement timepoint differed (36 months in HELIOS-B vs 30 months ATTR-ACT) and a numerical comparison of the point estimate of HR in each trial would likely be insufficient grounds to establish non-inferiority.

Network meta-analysis comparing vutrisiran from HELIOS-B to tafamidis from ATTR-ACT

6.31 The NICE evaluators conducted a network meta-analysis (NMA) that compared the vutrisiran monotherapy arm from HELIOS-B to the tafamidis arm from ATTR-ACT and to real-world data from the THAOS registry which led to ACM HRs of 0.89 (95% CI 0.53, 1.43) and 1.17 (95% CI 0.73, 1.90), respectively (HR < 1 favoured the vutrisiran arm; pp343-5, Vutrisiran TA115 NICE Committee Papers 2026). The interpretation of results may be limited since differences in baseline patient characteristics were not adjusted for.

MAIC of vutrisiran from HELIOS-B and tafamidis from ATTR-ACT

6.32 The Pre-PBAC Response included information from the MAIC of vutrisiran and tafamidis based on HELIOS-B and ATTR-ACT that was presented to NICE (see para 6.8). The results were broadly consistent with the IPTW results but were not evaluated due to the timing of receipt.

Comparative harms

6.33 An overview of adverse events (AE) from HELIOS-B and the tafamidis arms from ATTR-ACT is presented in Table 6.

6.34 Noting that the comparative safety assessment informing this submission was a *post hoc* non-randomised side by side comparison of the vutrisiran monotherapy subgroup from HELIOS-B with the tafamidis monotherapy subgroup from HELIOS-B and tafamidis groups from ATTR-ACT, the inferences of risk differences and relative risks were considered limited to informing a comparative safety assessment and are not presented.

Table 6: Summary of key AEs from HELIOS-B and tafamidis arms from ATTR-ACT

Event, n (%)	HELIOS-B				ATTR-ACT
	Overall		Vutrisiran monotherapy (N=196)[a]	Tafamidis monotherapy (N=129)[b]	
	Vutrisiran (N=326)	Placebo (N=328)			Pooled tafamidis (N=264)
Any AE	322 (98.8)	323 (98.5)	192 (98.0)	129 (100.0)	260 (98.5)
Treatment-related	41 (12.6)	46 (14.0)	18 (9.2)	23 (17.8)	113 (42.8)
Serious AE	201 (61.7)	220 (67.1)	112 (57.1)	85 (65.9)	164 (62.1)
Treatment-related	2 (0.6)	1 (0.3)	1 (0.5)	0 (0.0)	5 (1.9)
Severe AE	158 (48.5)	194 (59.1)	93 (47.4)	68 (52.7)	NR
Treatment-related	1 (0.3)	2 (0.6)	0 (0.0)	1 (0.8)	NR
AE leading to drug interruption	8 (2.5)	8 (2.4)	6 (3.1)	3 (2.3)	NR
Treatment-related	2 (0.6)	0 (0.0)	1 (0.5)	0 (0.0)	NR
AE leading to discontinuation	10 (3.1)	13 (4.0)	6 (3.1)	3 (2.3)	56 (21.2)
Treatment-related	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.8)	NR
AE leading to study withdrawal	2 (0.6)	6 (1.8)	1 (0.5)	2 (1.6)	NR
Treatment-related	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.8)	NR
Deaths	49 (15.0)	63 (19.2)	37 (18.9)	20 (15.5)	39 (14.8)
Serious AEs in ≥2% of patients					**Tafamidis 80mg (n=176)**
Cardiac failure	38 (11.7)	57 (17.3)	25 (12.8)	14 (10.9)	34 (19.3)
Atrial fibrillation	26 (8.0)	20 (6.1)	7 (3.6)	13 (10.1)	11 (6.3)
Cardiac failure acute	13 (4.0)	18 (5.5)	5 (2.6)	12 (9.3)	23 (13.1)
Pneumonia	12 (3.7)	10 (3.0)	5 (2.6)	4 (3.1)	13 (7.4)
Acute kidney injury	11 (3.4)	10 (3.0)	7 (3.6)	5 (3.9)	13 (7.4)

Source: Table 2-27, Table 2-28, p98, Table 2-31, p102, Table 2-43, p118; Table 2-45, p120 of the submission; Table 14.3.1.1 and Table 14.3.1.7 Attachment to the submission; Table 6, tafamidis PSD July 2023 PBAC Meeting

AE = adverse event; NR = not reported

[a] Vutrisiran monotherapy group (i.e., patients randomised to vutrisiran and had no baseline tafamidis use)

[b] Tafamidis monotherapy group (i.e., patients randomised to placebo and had baseline tafamidis use)

Notes:

Grey shaded cells indicate the groups that informed the *post hoc* stabilised IPTW analysis and the clinical claim.

Blue shaded cells indicate data or information previously presented to the PBAC.

6.35 The naïve comparison of groups within HELIOS-B suggested that the tafamidis monotherapy group experienced a higher proportion of serious AEs (65.9% [85/129] vs 57.1% [112/196]), severe AEs (52.7% [68/129] vs 47.4% [93/196]) and serious atrial fibrillation (10.1% [13/129] vs 3.6% [7/196]) compared to the vutrisiran monotherapy group.

6.36 The naïve comparison of vutrisiran monotherapy from HELIOS-B and tafamidis from ATTR-ACT suggested that a higher proportion of patients from the pooled tafamidis group experienced serious AEs (62.1% [164/264] vs 57.1% [112/196]) and AEs leading to discontinuation (21.2% [56/264] vs 3.1% [6/196]); and that a higher proportion of patients in the tafamidis 80 mg arm experienced serious cardiac failure (19.3% [34/176] vs 12.8% [25/196]), including acute cardiac failure (13.1% [23/176] vs 2.6% [5/196]), as well as serious atrial fibrillation (6.3% [11/176] vs 3.6% [7/196]).

6.37 The naïve comparison of safety outcomes should be interpreted with caution since patients in the tafamidis monotherapy group from HELIOS-B were already receiving tafamidis for a mean duration of 13.1 months at baseline, and patients in the vutrisiran monotherapy group had drop-in tafamidis which potentially confounded AE reporting

in the tafamidis monotherapy group and vutrisiran monotherapy group, respectively. Furthermore, the comparability of safety outcomes between HELIOS-B and ATTR-ACT was limited due to differences in patient characteristics and background care (see para. 6.18). Similar AEs were observed in the placebo monotherapy arm and overall treatment-related AEs were relatively low, it was also possible that some of these events were manifestations of ATTR-CM rather than due to treatment.

Benefits/harms

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

Clinical claim

6.39 The submission described vutrisiran as non-inferior in terms of effectiveness compared to tafamidis. The evaluation considered the claim may not be adequately supported due to inherent uncertainties in the presented evidence. The *post hoc* stabilised IPTW analysis that compared the vutrisiran monotherapy group and tafamidis monotherapy group from HELIOS-B, was considered uncertain with questionable generalisability as:

- Although the IPTW adjusted for 12 characteristics and produced effective sample sizes comparable to the original sample, the ESC considered the non-randomised design means that unmeasured confounding cannot be ruled out.
- The analysis was a *post hoc* non-randomised comparison that may not have sufficient statistical power to detect non-inferiority. The ESC agreed with concerns related to low power. Additionally, the ESC agreed that concern regarding the non-randomised nature and uncertainty of the indirect comparison was justified, however, acknowledged that the IPTW presented in the submission solely used data from the HELIOS-B trial, which mitigates any potential between-trial variability that may arise from using the ATTR-ACT trial. At the non-inferiority margin of 1.1 at the upper 95% CI (noted but not applied in the submission), non-inferiority of the primary composite endpoint and ACM would not be met (i.e., the upper 95% CI of 1.29 and 1.34 exceeded 1.1).
- Applicability of treatment utilisation to clinical practice was lacking or unclear as:
    - Tafamidis dosage and compliance in the tafamidis monotherapy group was not reported which made it unclear as to whether results from this subgroup would be generalisable to patients treated with tafamidis in the proposed population. While the ESC accepted the PSCR's claim that tafamidis was dosed in accordance with global regulatory conditions consistent with the Australian registration, the ESC noted further treatment details including compliance and duration would have been informative.
    - Drop-in/add-on concomitant tafamidis would not be permitted under the requested restriction and the lack of accounting for its use in the vutrisiran

monotherapy group potentially biased the treatment effect in favour of vutrisiran.

- The proportion of concomitant SGLT-2 inhibitor use in HELIOS-B was unlikely to reflect potentially higher use in the proposed PBS population where it remained unclear if a treatment interaction with vutrisiran exists (including potential safety interactions).
- It was unclear if patients classified as NYHA Class III with NAC stage 1 or 2 in the tafamidis monotherapy group were excluded from the stabilised IPTW analysis. These patients would not be eligible for PBS subsidised tafamidis in clinical practice and including these patients potentially biased the comparison against tafamidis. The PSCR presented further information regarding the IPTW analysis, noting that NYHA Class III patients were included in the comparison. However, ESC judged that, given Class III patients represented only 7.5% of the cohort, their inclusion was unlikely to have introduced significant bias.
- Vutrisiran could be used beyond progression to NYHA Class III and NAC stage 3 and NYHA Class IV in HELIOS-B whereas these patients would not be eligible for treatment under the requested restriction which potentially overestimated the treatment effect of vutrisiran.

- The appropriate comparator for patients with NYHA Class III and NAC stage 1 or 2 would be BSC, which was not adequately supported by subgroup data of HELIOS-B, and the presented analyses suggest there is insufficient data to robustly inform such a comparison.

6.40 Overall, the ESC considered the claim of non-inferior comparative effectiveness to be uncertain and not well established based on the stabilised IPTW analysis, however considered the totality of the available evidence was suggestive of a similar treatment effect for vutrisiran and tafamidis in ATTR-CM.

6.41 The submission described vutrisiran as non-inferior in terms of safety compared to tafamidis. The evaluation considered the claim was unable to be reliably informed by the naïve comparisons of monotherapy groups within HELIOS-B, and the comparison using ATTR-ACT was potentially confounded due to differences in baseline patient characteristics (e.g., proportion of NYHA Class III and NAC stage 3, and duration of disease) and background care. The ESC considered that while the claim was uncertain based on the naïve comparisons, no significant safety issues of concern were identified and overall may be reasonable.

6.42 For patients with NYHA Class I and II disease, the PBAC considered that the claim of non-inferior comparative effectiveness and safety was adequately supported by the data.

6.43 The PBAC considered that tafamidis was not an appropriate comparator for patients with Class III disease with NAC stage 1 or 2, and therefore the submission's claim of

non-inferior comparative effectiveness and safety compared with tafamidis in this population was not relevant.

Economic analysis

6.44 The submission adopted a CMA based on the clinical claim that vutrisiran was non-inferior in terms of efficacy and safety compared to tafamidis as informed by a *post hoc* stabilised IPTW analysis from HELIOS-B and naïve comparisons of HELIOS-B and ATTR-ACT.

6.45 The key components and assumptions of the CMA are presented in Table 7.

Table 7: Key components and assumptions of the CMA

Component	Claim or assumption
Therapeutic claim: effectiveness	Effectiveness is assumed to be non-inferior.
Therapeutic claim: safety	Safety is assumed to be non-inferior.
Evidence base	Efficacy was informed by a *post hoc* stabilised IPTW analysis of the vutrisiran monotherapy group compared to the tafamidis monotherapy group from HELIOS-B. Safety was informed by a naïve comparison of the vutrisiran monotherapy group and tafamidis monotherapy group from HELIOS-B and the pooled tafamidis group from ATTR-ACT.
Equi-effective doses	Vutrisiran 25 mg SC injection Q3M = Tafamidis 61 mg orally OD[a]
Direct medicine costs	Vutrisiran placeholder effective AEMP = $31,890.73 Tafamidis published AEMP = $9,860.00
Other costs or cost offsets	Administration costs of vutrisiran, MBS item 3 = $20.50[b]

Source: Table 3-1, p129 of the submission

AE = adverse event; AEMP = approve ex-manufacturer price; CMA = cost minimisation approach; SC = subcutaneous; OD = once daily; Q3M = once every three months.

[a] Equivalent to tafamidis meglumine 80 mg

[b] The submission briefly discussed costs for screening or monitoring tests, concomitant medication, and AE management but assumed a zero cost for these items in the CMA.

6.46 The equi-effective doses were estimated as vutrisiran 25 mg Q3M and tafamidis 61 mg OD. The submission based the CMA on cost of treatment over one year and assumed that both treatments were continued on an ongoing basis with no treatment discontinuation, and compliance rates of 92.90% and 97.67% for vutrisiran and tafamidis, respectively. The ESC noted the PBAC recommended vutrisiran for hATTR-PN based on equi-effective doses with 12 weekly treatment rather than Q3M and considered given the dosing of vutrisiran in HELIOS-B was every 12 weeks +/- 7 days that it was more appropriate for the equi-effective dose component of vutrisiran to also be based on 12-week dosing for ATTR-CM (see sensitivity analyses below).

6.47 The dose and frequency of vutrisiran (Q3M) was consistent with the HELIOS-B trial and the recommended doses from the vutrisiran PI. However, the HELIOS-B CSR (Section 9.4.1) additionally specified that dosing occurred “every 12 weeks ± 7 days” which suggested that dosing potentially occurred on a more frequent basis (i.e., 52/12 weeks equated to 4.33 doses per year instead of four doses per year assumed by the submission). The Pre-PBAC Response reiterated the dosing interval in HELIOS-B was 12 weeks ± 7 days, which is up to 91 days or equivalent to Q3M and argued it was therefore appropriate for the CMA.

6.48 The tafamidis dose received by patients in the tafamidis monotherapy group from HELIOS-B was unknown, as dosing depended on 'the recommended dose in the patient's local jurisdictions' which was not explicitly reported. This potentially presented an applicability concern to clinical practice noting that only the tafamidis 61 mg formulation is currently PBS listed. Based on the global data from the THAOS registry of ATTR-CM patients treated with tafamidis between 2007 and 2023 (N=587), the majority of patients received tafamidis 80/61 mg or titrated up from 20 mg to 80/61 mg (89.9% [528/587]) vs 8.8% [52/587] received tafamidis 20 mg and 2.1% [7/587] received another unspecified dose (Garcia-Pavia 2025).[20]

6.49 Treatment discontinuation for both vutrisiran and tafamidis were assumed to be 0% which was not consistent with the HELIOS-B or ATTR-ACT trials, nor would this be applicable to clinical practice. Treatment discontinuation was 23.9% (78/326) in the vutrisiran arm from HELIOS-B, while treatment details were not reported for the tafamidis monotherapy group. In the tafamidis submission which was informed by the ATTR-ACT trial, treatment discontinuation was 19.6% (52/264) in the pooled tafamidis group from the trial. However, the trials durations were substantially longer than one year, and it may have been more appropriate to conduct the CMA over a longer time horizon (e.g., consistent with the trial period) to appropriately capture treatment discontinuation. The Pre-PBAC Response acknowledged discontinuations were not considered in the CMA, however argued they would be difficult to reliably include, as the trial durations were different (36 months for HELIOS-B, 30 months for ATTR-ACT) and only total discontinuations were reported, which would require estimating a monthly discontinuation rate to account for in the CMA. The Response argued it may be reasonable to maintain a simple approach of assuming no difference in discontinuations for the CMA.

6.50 The compliance rate of vutrisiran was based on the vutrisiran arm from the overall population of HELIOS-B and reflected patients who had no missed doses of the study drug (303/326 [92.9%]). This compliance rate potentially underestimated the vutrisiran utilisation as it did not account for patients from HELIOS-B who only missed one (16/326 [4.9%]) or two doses (7/326 [2.1%]) and applying dose intensities may better capture the compliance of these patients. In comparison, in the tafamidis submission, compliance was based on dose intensities from ATTR-ACT (para. 6.40, tafamidis PSD July 2023 PBAC Meeting). Though, as with treatment discontinuation rates, it was unclear how applicable this compliance rate was to the tafamidis monotherapy group in HELIOS-B which informed this submission as details within this group were minimally reported. The ESC considered it was implausible that there would be lower compliance in practice with vutrisiran as a once every 3 month injection, compared to tafamidis as a daily tablet and therefore advised the CMA

[20] Garcia-Pavia P, et al. (2025). Survival in a Real-World Cohort of Patients With Transthyretin Amyloid Cardiomyopathy Treated With Tafamidis: An Analysis From the Transthyretin Amyloidosis Outcomes Survey (THAOS). Journal of Cardiac Failure; 31, 525-533

should be adjusted to assume equivalent compliance (or remove the compliance modifier entirely) (see sensitivity analyses below). The Pre-PBAC Response argued it may be simpler (alongside discontinuations noted above) to assume equal compliance with vutrisiran and tafamidis.

6.51 The submission only included additional costs for vutrisiran associated with SC administration. The submission applied the MBS item 3 fee of $20.05 (100% MBS benefit) to reflect the average cost of SC administration of vutrisiran by healthcare professionals or trained caregivers/patients (no administration cost). The proportion of doses that would be administered via caregiver/patient was unclear; hence the evaluation considered it was unclear whether MBS item 3 was appropriate. The evaluation noted that MBS item 116 was used in the vutrisiran submission for hATTR-PN (Table 10, vutrisiran [hATTR-PN] PSD, November 2024 PBAC meeting), and the relevant fee was $89.40.

6.52 The submission did not include additional costs for vitamin A supplementation, monitoring or testing from treatment, and AE management costs. Of note, while the evidence to inform the claim of non-inferior safety was uncertain (see para. 6.40), treatment-related AEs in HELIOS-B for patients in vutrisiran monotherapy (9.2% [18/196]) and tafamidis monotherapy (17.8% [23/129]) groups were relatively low. Injection site reactions were also low in patients who received vutrisiran in HELIOS-B (<3%) and as such, the omission of costs of managing AEs was likely reasonable.

6.53 The published AEMP of tafamidis was $9,860.00 (DPMQ $10,022.93) and the recommended dose was tafamidis 61 mg capsule orally OD. Tafamidis 61 mg OD would be administered 365.25 times per year and requiring 12.175 packs. Vutrisiran SC Q3M would be administered four times per year.

6.54 The submission's results of the CMA based on the placeholder effective AEMP of vutrisiran are presented in Table 8.

Table 8: CMA results from the submission – placeholder effective price of vutrisiran and published price of tafamidis

Component	Vutrisiran	Tafamidis
Inputs		
Dosing regimen	25 mg Q3M	61 mg OD
Doses per year	4	365.25
Maximum quantity	1	30
Units/packs per year	4	12.175
AEMP	$31,890.73	$9,860.00
Fees and mark ups[a]	$162.93	$162.93
DPMQ	$32,053.66	$10,022.93
Cost per administration	$20.05	$0
Adherence	92.90%	97.67%
Results		
Cost per dose	$32,053.66	$334.10
Total drug cost/year[b]	$128,214.63	$122,029.17
Total administration cost/year	$80.20	$0
Total cost per year[c]	**$119,185.89**	**$119,185.89**
Difference in cost per year[d]	**$0**	

Source: Table 3-4 and 3-5, pp134-5 of the submission
AEMP = approved ex-manufacturer price; CMA = cost-minimisation approach; DPMQ = dispensed price for maximum quantity; OD = once daily; Q3M = once every three months.
[a] Fees and mark ups as of 1 December 2025 (dispensing fee = $8.88; wholesale markup = $54.14; AHI fee = $99.91)
[b] Assumed ongoing treatment and 0% discontinuation in both treatment arms.
[c] Adherence rates applied.
[d] Difference of vutrisiran cost – tafamidis cost

6.55 The submission estimated the total annual cost of tafamidis was $119,185.89 and the CMA resulted in the placeholder effective AEMP for vutrisiran of $31,890.73 (DPMQ $32,053.66).

6.56 Scenario analyses based on the submission's placeholder effective prices are presented in Table 9.

Table 9: Scenario analyses – placeholder prices from the submission

Component	Annual cost $			Placeholder Vutrisiran Effective price	%Δ
	Tafamidis	Vutrisiran	Δ[a]		
Base case	$119,186	$119,186	$0	$31,890.73	-
Additional sensitivity analyses conducted during the evaluation					
Assumed 100% compliance for both treatments[c]	$128,295	$122,029	+$6,266	$30,324.31	-4.9%
Assumed vutrisiran every 12 weeks as per clinical trial	$119,186	$129,118	+$9,932	$29,423.52	-8.8%
Administration cost = $89.40 (MBS item 116)	$119,442	$119,186	+$256	$31,821.38	-0.2%

Source: calculated during the evaluation based on tafamidis effective prices from 1 May 2026
AEMP = approved ex-manufacturer price; CPI = Consumer Price Index; MBS = Medicare Benefits Schedule; 1PWA = First Pharmaceutical; Wholesaler Agreement
[a] Difference = total costs of vutrisiran – total costs of tafamidis
[c] Base case compliance rates: vutrisiran = 92.90%, tafamidis = 97.67%
Notes:
% Δ = percentage change from base case placeholder effective price of vutrisiran
Italicised text indicates additional analyses conducted during the evaluation
Vutrisiran was cost minimised against tafamidis.

6.57 The CMA of vutrisiran compared to tafamidis may not be applicable to ATTR-CM patients classified as NYHA Class III with NAC stage 1 or 2 since tafamidis was not the appropriate comparator for this subgroup (see para. 5.3). The ESC noted that cost

effectiveness has not previously been established by the PBAC for tafamidis in patients with NYHA Class III and therefore considered a CMA approach was not appropriate for this population. The Pre-PBAC Response advised that given the comparatively small proportion of patients with NYHA Class III and limited data that it would not be feasible to undertake a modelled evaluation for this population.

Drug cost/patient/year

6.58 Drug cost per patient per year for vutrisiran and tafamidis using the placeholder effective price and published price, respectively, is presented in Table 10.

Table 10: Drug cost per patient per year for vutrisiran and tafamidis

	HELIOS-B	CMA	Financials
Vutrisiran 25 mg/0.5 ml pre-filled syringe (placeholder effective price)			
Dosing regimen	25 mg Q3M	25 mg Q3M	25 mg Q3M
Drug cost per injection	-	$32,053.66 (DPMQ)	$32,053.66 (DPMQ)
Cost per administration	-	$20.50 ($100% MBS benefit)	$16.40 (80% MBS benefit)
Doses per year	4	4	4
Units	1	1	1
Compliance	92.90%	92.90%	92.90%
Persistence	23.90% discontinued	0% discontinuation	0% discontinuation
Cost per year	-	$119,185.89	$119,172.33
Tafamidis 61 mg capsules (published price)			
Dosing regimen	NR	61 mg OD	61 mg OD
Drug cost per pack	-	$10,022.93 (DPMQ)	$10,022.93 (DPMQ)
Cost per administration	-	$0	$0
Doses per year	365.25	365.25	365.25
Units per pack	30	30	30
Compliance	97.67%	97.67%	97.67%
Persistence	NR	0% discontinuation	0% discontinuation
Cost per year	-	$119,185.89	$119,185.89

Source: Table 3-4 and 3-5, pp134-5 of the submission
CMA = cost-minimisation approach; DPMQ = dispensed price for maximum quantity; MBS = Medicare Benefits Schedule; NR = not reported; OD = once daily; Q3M = once every three months.
Notes:
Cost per year = (drug cost + administration cost) × (doses per year ÷ units) × compliance rate × persistence rate

6.59 Based on the placeholder effective price of vutrisiran ($31,890.73) and the published price of tafamidis ($9,860.00), the cost per year of vutrisiran was $119,185.89 in the CMA and $119,172.33 in the financials. This difference was due to the CMA applying the 100% MBS benefit whereas the financials applied the 80% benefit for the cost of administering vutrisiran. The cost per year of tafamidis was $119,185.89 in both the CMA and financial estimates.

Estimated PBS usage & financial implications

6.60 This submission was not considered by the DUSC.

6.61 The submission used a prevalence-based epidemiological approach. The submission stated that vutrisiran is expected to substitute for tafamidis; however the submission estimated growth in the treated population and additional cost associated with the

requested listing for NYHA Class III with NAC stage 1 or 2, for whom tafamidis is not available on the PBS.

6.62 The key inputs and sources of the financial estimates is presented in Table 11.

Table 11: Inputs and assumptions of the epidemiological approach

Parameter	Value	Source	Comment
Population: ATTR-CM			
Prevalence	224 per million.	Laires 2025. A retrospective analysis of US electronic health records database between 2016 and 2023. A prevalence of 224 per million was reported based on 81,935 ATTR-CM cases in the US identified using the 'broad definition'.[a] Patients with light chain amyloidosis or multiple myeloma were excluded.	Laires 2025 had uncertain applicability to Australian prevalence. Reliable prevalence studies in the Australian population were lacking, and prevalence remains unclear but there may be sentiment that ATTR-CM is an underdiagnosed disease (para. 7.16, tafamidis PSD, July 2020 PBAC meeting)
% Hospitalisation for heart failure or heart failure requiring diuretic treatment	100%.	Assumption based on Healy 2025 and Nies 2025. Healy 2025 prospectively screen for ATTR-CM in an undifferentiated cohort of patients with heart failure with preserve ejection fraction (N=86). Healy 2025 reported that 4/7 (57%) ATTR-CM patients had previous hospitalisation due to heart failure at baseline Nies 2025 was a retrospective, single-cohort study of ATTR-CM patients in Germany between 2020 and 2023 (n=182), and reported 36/182 (20%) had a history of hospitalisation due to heart failure. 58.8% (107/182) reported to receive any dose of furosemide and 51.1% (93/182) reported receiving a non-loop diuretic at baseline but it was unclear if all patients had diuretics.	Healy 2025 and Nies 2025 did not adequately support an assumption of 100% having had hospitalisation for heart failure or heart failure requiring diuretic. Based on a THAOS registry study, among wildtype and hereditary ATTR patients with predominantly cardiac or mixed phenotype, heart failure was reported in 87% (1,227/1,410) and 72% (787/1,088), respectively; Gentile 2023).[21]

[21] Gentile L, et al. (2023). A 15-year consolidated overview of data in over 6000 patients from the Transthyretin Amyloidosis Outcomes Survey (THAOS). Orphanet J Rare Dis 18, 350 (2023). https://doi.org/10.1186/s13023-023-02962-5

Parameter	Value	Source	Comment
% Interventricular end diastolic septal wall ≥12 mm	100%.	Assumption based on Geenty 2025, Cuscaden 2021, and Nies 2025. Geenty 2025 was a prospective survey of patients with ATTR-CM in seven specialist clinics across Australia and New Zealand in 2022 (N=515). The mean IVSd was 16 mm and 14 mm in ATTRwt and hATTR patients, respectively. Cuscaden 2021 reported on incidental findings of ATTR-CM in an Australian subpopulation using bone scintigraphy (n=6,918) and stated that all patients with ATTR-CM findings (15/6,918) had 'increased septal wall thickness'. The average IVSd was not reported. Nies 2025 (n=182) reported a median IVSd of 17 mm.	There may be some patients with ATTR-CM of whom have wall thickness less than 12 mm (e.g., females) who would not be eligible for treatment, thus the 100% proportion may be overestimated but the magnitude was not clear.
% eGFR ≥25 mL/min/1.73 m^2	100%.	Assumption based on Ioannou 2024 and Nies 2025. Ioannou 2024 was a retrospective longitudinal study of ATTR-CM patients between 2005 and 2022 (N=2,275) and reported mean eGFRs between 62 and 81 mL/min/1.73 m^2. Nies 2025 (n=182) reported a mean eGFR of 58 mL/min/1.72 m^2.	The mean eGFR levels exceeded ≥25 mL/min/1.73 m^2 in these studies, this was similarly observed in the Australian and New Zealand cohort from Geenty 2025 (mean eGFR ranged from 61 and 79 mL/min/1.73 m^2).
% NYHA I, II, or III + NAC 1 or 2	NYHA Class I or II = 73.90%. NYHA Class III + NAC 1 or 2 = 15.71%. Total = 89.61%.	Nitsche 2024 was a retrospective study of ATTR-CM patients between 2005 and 2022 that reported on NYHA class alongside NAC staging (N=2,042). Based on non-missing data, 12.14% (231/1,903) had NYHA I, 61.75% (1,175/1,903) had NYHA II, and 15.97% (304/1,903) had NYHA Class III with NAC stage 1 or 2.	There was a slight inconsistency in the proportion of NYHA Class III with NAC stage 1 or 2 in the submission (15.71%) compared to Nitsche 2024 (15.97% [304/1,903]). This difference could not be reconciled.
% Treatment Uptake Rate	Yr 1 = [redacted]%. Yr 2 = [redacted]%. Yr 3-6 = [redacted]%.	Commercial forecast based on overseas experience.	Relatively low despite vutrisiran proposed as the only disease modifying treatment alternative to tafamidis, the only treatment for patients with NYHA Class III with NAC stage 1 or 2, and improved adherence due to less frequent dosing.
Grandfathered patients	Included in prevalent population.	Assumption.	The evaluation considered this was reasonable.

Parameter	Value	Source	Comment
Treatment utilisation			
% Compliance	Vutrisiran = 92.90%.	Based on the proportion of patients who did not miss any dose of vutrisiran from HELIOS-B (Section 10.4 HELIOS-B CSR)	Potentially underestimated as it excluded patients with any missed dose. May underestimate vutrisiran utilisation.
	Tafamidis = 97.67%.	Based on dose intensities of tafamidis from ATTR-ACT (Table 10, tafamidis PSD, July 2023)	Unclear applicability to the tafamidis monotherapy group in HELIOS-B. If overestimated, will overestimate cost offsets from tafamidis.
% Discontinuation rate	Ongoing treatment with 0% discontinuation.	Assumption.	Inconsistent with HELIOS-B and ATTR-ACT and not representative of clinical practice. Potentially overestimated utilisation in both treatments.
Dosage Regimen	Vutrisiran 25 mg SC injection Q3M Tafamidis 61 mg orally OD.	Vutrisiran PI, HELIOS-B, tafamidis PI.	
Vutrisiran prices	Published: $114,121.96 AEMP $114.284.89 DPMQ Placeholder effective $31,890.73 AEMP $32,053.66 DPMQ	Based on published prices for vutrisiran. Placeholder effective prices based on published price of tafamidis.	
Tafamidis prices	Published: $9,860.00 AEMP $10,022.96 DPMQ.	Based on published prices for tafamidis. Effective prices were not known the Sponsor at the time of the evaluation.	
MBS costs	Administration cost = $20.05 in vutrisiran only.	Assumed MBS item 3 represented the average administration cost for vutrisiran via healthcare profession or caregiver/patient. 80% benefit applied.	The proportion of administrations via caregiver/ patient was not clear thus the applicability of MBS item 3 unclear. Sensitivity analysis applying MBS item 116 benefits (attendance by specialist) conducted during evaluation
Co-payments	PBS = $7.68 RPBS = $3.91	Average patient co-payment per 2025 PBS/RPBS utilisation of tafamidis (item 14100D) (proportion split 97.29% and 2.71% respectively)	
Substitution rates	Vutrisiran substituted for tafamidis in NYHA Class I or II patients (corresponding to 82.47% of vutrisiran patient pool).	Calculated as the number of NYHA Class I or II patients divided by the number of NYHA I, II, or III + NAC stage 1 or 2 patients from Nitsche 2024 (1,406/1,710).	

Source: Table 4-1, p140 of the submission.

AEMP = approved ex-manufacturer price; CMA = cost-minimisation approach; DPMQ = dispense price for maximum quantity; eGFR = estimated glomerular filtration rate; IVSd = interventricular septal wall thickness in diastole; MBS = Medicare Benefits Schedule; NAC = National Amyloidosis Centre; NYHA = New York Heart Association; OD = once daily; PBS = Pharmaceutical Benefits Scheme; PI = Product Information; PSD = Public Summary Document; Q3M = once every three months; RPBS = Repatriation Pharmaceutical Benefits Scheme; THAOS = Transthyretin Amyloidosis Outcomes Survey.

OFFICIAL

[a] ATTR-CM defined as a patient with one claim of amyloidosis, heart failure, and CM; or a SNOMED broad code for ATTR-CM; or physician notes for ATTR- CM; or a drug treatment code for ATTR- CM.

6.63 The evaluation noted minor inaccuracies in the submission's estimates of patient numbers and vutrisiran scripts and presented revised estimates (see footnotes of Table 11 for the changes conducted during the evaluation).

6.64 Since tafamidis would only be a cost offset to vutrisiran in the NYHA Class I or II subgroup, the evaluation separated the financial estimates by NYHA Class I or II and NYHA Class III with NAC stage 1 or 2 subgroups.

6.65 The estimated extent of use and net cost of vutrisiran to the PBS/RPBS and MBS using the placeholder effective price of vutrisiran and published price of tafamidis is presented in Table 11.

OFFICIAL

Table 11: Estimated use and financial implications - placeholder effective price vutrisiran and published price tafamidis

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients treated	[redacted]1	[redacted]2	[redacted]2	[redacted]2	[redacted]2	[redacted]2
NYHA I or II	[redacted]1	[redacted]2	[redacted]2	[redacted]2	[redacted]2	[redacted]2
NYHA III + NAC 1/2	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1
Number of scripts dispensed[a]	[redacted]2	[redacted]2	[redacted]2	[redacted]2	[redacted]2	[redacted]2
Estimated financial implications of vutrisiran						
Cost to PBS/RPBS less copayments	[redacted]7	[redacted]9	[redacted]11	[redacted]11	[redacted]11	[redacted]11
NYHA I or II	[redacted]6	[redacted]8	[redacted]10	[redacted]10	[redacted]10	[redacted]10
NYHA III + NAC 1/2	[redacted]3	[redacted]4	[redacted]4	[redacted]4	[redacted]5	[redacted]5
Estimated financial implications for tafamidis						
Cost to PBS/RPBS less copayments	[redacted]6	[redacted]8	[redacted]10	[redacted]10	[redacted]10	[redacted]10
NYHA I or II	[redacted]6	[redacted]8	[redacted]10	[redacted]10	[redacted]10	[redacted]10
NYHA III + NAC 1/2	[redacted]3	[redacted]3	[redacted]3	[redacted]3	[redacted]3	[redacted]3
Net financial implications						
Net cost to PBS/RPBS	[redacted]3	[redacted]4	[redacted]4	[redacted]4	[redacted]5	[redacted]5
NYHA I or II	[redacted]3	[redacted]3	[redacted]3	[redacted]3	[redacted]3	[redacted]3
NYHA III + NAC 1/2	[redacted]3	[redacted]4	[redacted]4	[redacted]4	[redacted]5	[redacted]5
Net cost to MBS	[redacted]3	[redacted]3	[redacted]3	[redacted]3	[redacted]3	[redacted]3
NYHA I or II	[redacted]3	[redacted]3	[redacted]3	[redacted]3	[redacted]3	[redacted]3
NYHA III + NAC 1/2	[redacted]3	[redacted]3	[redacted]3	[redacted]3	[redacted]3	[redacted]3
Net cost to health budget	[redacted]3	[redacted]4	[redacted]4	[redacted]4	[redacted]5	[redacted]5
NYHA I or II	[redacted]3	[redacted]3	[redacted]3	[redacted]3	[redacted]3	[redacted]3
NYHA III + NAC 1/2	[redacted]3	[redacted]4	[redacted]4	[redacted]4	[redacted]5	[redacted]5

Source: '3a Scripts – proposed', '3c. Impact – proposed (eff)', '4a Scripts – affected', '4c. Impact – affected (eff)', '5. Impact – net', '7. Net changes - MBS' worksheet from the financial workbook

ATTR-CM transthyretin amyloidosis with cardiomyopathy; eGFR = estimated glomerular filtration rate; IVSd = interventricular septal wall thickness in diastole; MBS = Medicare Benefits Schedule; NAC = National Amyloidosis Centre; NYHA = New York Heart Association; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme; Pts = patients

[a] Assuming 3.72 per year as estimated by the submission

Note.

Revisions of the financial estimates conducted during the evaluation

- The proportion of NYHA I, II, and III + NAC stage 1 or 2 as reported from Nitsche 2024 were accurately applied which led to slightly higher patient numbers. From Nitsche 2024, the proportion of NYHA I or II = (231+1175) ÷ 1903; and the proportion of NYHA III + NAC 1/2 = 304 ÷ 1903.
- In the vutrisiran script calculations, the dose per period was estimated using the formula '1/3' which resulted in 3.72 scripts per year compared to the submission which applied the raw data value of '0.33' and resulted in 3.69 scripts per year.

The redacted values correspond to the following ranges:

[1] < 500
[2] 500 to < 5,000
[3] $0 to < $10 million
[4] $10 million to < $20 million
[5] $20 million to < $30 million
[6] $40 million to < $50 million
[7] $50 million to < $60 million
[8] $60 million to < $70 million
[9] $80 million to < $90 million
[10] $90 million to < $100 million
[11] $100 million to < $200 million

6.66 It was estimated that there would be < 500 patients treated with vutrisiran in Year 1 (2027) and increasing to 500 to < 5,000 patients in Year 6 (2032). This comprised of <

500 patients with NYHA Class I or II and < 500 patients with NYHA Class III with NAC stage 1 or 2 in Year 1, and increasing to 500 to < 5,000 patients and < 500 patients, respectively, in Year 6. These numbers assumed that 73.8% and 15.9% of ATTR-CM patients were classified as NYHA Class I or II and NYHA Class III with NAC stage 1 or 2, respectively (Nitsche 2024).

6.67 The key driver of the cost was the utilisation in patients with NYHA Class III with NAC stage 1 or 2, for whom tafamidis is not available on the PBS.

6.68 Based on the placeholder effective price, in the NYHA Class I or II subgroup the net cost to the health budget was $0 to < $10 million over six years. Notably the CMA derived effective price of vutrisiran was based on an MBS benefit of 100% for administration costs compared to the 80% benefit applied in the financials. In a sensitivity analysis that assumed a 100% MBS benefit, the net cost after accounting for the difference in co-payments was effectively zero.

6.69 The evaluation considered the submission's financial estimates may be underestimated noting that the prevalence of ATTR-CM is highly uncertain and the PBAC has previously considered ATTR-CM to be an underdiagnosed disease; and the uptake of vutrisiran in clinical practice may be higher than estimated in the base case given that vutrisiran is positioned as the only disease-modifying treatment alternative to tafamidis and the only treatment for patients with NYHA Class III with NAC stage 1 or 2. The evaluation also considered vutrisiran may have improved adherence given its less frequent dosing schedule. The ESC considered the magnitude of underestimation remained unclear. The Pre-PBAC Response agreed the financial estimates may be underestimated, even using the most contemporary epidemiological evidence available, and based on the survey of 30 Australian clinical experts estimated a local prevalence of 435 per million (compared to 224 per million in the submission base case).

6.70 The evaluation noted additional uncertainty with the financial estimates since treatment discontinuation was assumed to be 0% which potentially overestimated treatment utilisation of both vutrisiran and tafamidis.

6.71 The ESC considered that patient numbers were underestimated and likely to be higher due to uncertain prevalence, underestimated uptake, lack of consideration of sequential use and the possibility for patient or clinician preference for 12-week dosing.

6.72 The proportion of patients with mixed phenotypes was not considered by the submission, which may result in an overestimate of the utilisation of vutrisiran as some mixed phenotype patients may already be treated under the hATTR-PN PBS listing. This might represent a sizeable proportion according to the THAOS registry study by Gentile 2023 (see para. 4.3), which reported that among hATTR patients with cardiac symptoms more than two-thirds (68.8% [748/1,088]) had mixed phenotype. Noting the low prevalence of hATTR-PN, the ESC considered that a small number of patients would be impacted by this concern.

Quality Use of Medicines

6.73 The submission stated that no specific quality use of medicines issues has been identified.

Financial Management – Risk Sharing Arrangements

6.74 The submission did not propose joining any existing Risk Sharing Arrangement (RSA) framework but indicated the sponsor was willing to work with the PBAC and the Department should the PBAC recommend implementation of an RSA.

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

7 PBAC Outcome

7.1 The PBAC recommended the listing of vutrisiran for the treatment of patients with wildtype or hereditary transthyretin amyloidosis with cardiomyopathy (ATTR-CM) with New York Heart Association (NYHA) Class I and II disease on a cost minimisation basis with tafamidis. For patients with NYHA Class I and II disease, the PBAC considered that the claim of non-inferior comparative effectiveness and safety was adequately supported by the data.

7.2 The PBAC noted that the submission had also requested listing for vutrisiran for patients with NYHA Class III disease with National Amyloidosis Centre (NAC) Stage I or II. The PBAC considered that use of vutrisiran in patients with NYHA Class I and II disease appeared to be clinically appropriate on the basis that the goal of treatment of patients with less severe disease at baseline would be to reduce progression to higher NYHA classes. The PBAC did not recommend PBS listing for this population because the cost-effectiveness of vutrisiran could not be assessed based on the information provided in the submission.

7.3 The PBAC advised the equi-effective doses were one injection of vutrisiran 25 mg every 12 weeks and tafamidis 61 mg capsule given once daily.

7.4 The PBAC considered there was a modest clinical need for additional effective therapies for ATTR-CM, noting tafamidis was generally effective and well tolerated, but that it would be beneficial for an additional treatment option with a different mechanism of action to be available on the PBS.

7.5 The PBAC welcomed input from individuals and organisations supporting the listing. The input highlighted the severe impact of ATTR-CM on quality of life and the importance of additional treatment options, especially for patients who do not adequately respond to or cannot tolerate tafamidis.

7.6 The PBAC considered that clinical practice has changed and diagnosis of ATTR-CM is occurring earlier in the disease process than occurred previously due to increased use of bone scans (para 4.7). The PBAC also noted the rate of ATTR-CM diagnosis in Australia indicates the condition is substantially more common than originally

anticipated, and it was unclear whether historical clinical trial populations are representative of patients identified in current clinical practice. The PBAC noted that additional clinical input was sought before the PBAC considered this submission. The consultation focused on treatment practices and clinical management of ATTR-CM.

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

- A Section 85 General Schedule, Authority Required (Written) listing for the first PBS-subsidised prescription and an Authority Required (Telephone/Online) for the second and subsequent PBS-subsidised prescription, consistent with the listing of tafamidis
- A maximum quantity of one with one repeat, providing 6 months of therapy
- Listing should be restricted to NYHA Class I and II (see paragraph 3.3, 7.1 and 7.2)
- A minimum eGFR requirement of 30mL/min/1.73m^2 (consistent with the trial inclusion criteria and TGA-approved Product Information for vutrisiran)
- Include criteria preventing combination use of vutrisiran and tafamidis (but allow switching between vutrisiran and tafamidis). The PBAC noted that flow-on changes would be required for tafamidis to include a clause that excludes combination therapy with vutrisiran and tafamidis.
- Include diagnostic criteria and discontinuation criteria aligned with the listing of tafamidis.
- Include a grandfather criteria in the initial listing
- An age-agnostic listing

7.8 The PBAC considered the nominated comparator of tafamidis, as the only PBS-listed therapy for ATTR-CM, was appropriate for patients with NYHA Class I and II disease. For patients with NYHA Class III disease with NAC stage 1 or 2, the PBAC considered that tafamidis was not an appropriate comparator, and that a clinical and economic evaluation comparing vutrisiran and best supportive care (BSC) would be required to support PBS listing for this indication.

7.9 The PBAC noted the submission was supported by two key trials: HELIOS-B, the pivotal placebo-controlled randomised trial of vutrisiran for ATTR-CM, and ATTR-ACT, the tafamidis randomised trial which had been used to support the earlier tafamidis applications. The PBAC noted the submission almost entirely relied upon HELIOS-B to inform the clinical claims. Rather than presenting a formal indirect treatment comparison of vutrisiran and tafamidis using the available evidence from both trials, the submission relied upon a stabilised inverse probability of treatment weights (IPTW) analysis of the vutrisiran arm (without concomitant tafamidis at baseline) versus a cohort of patients in HELIOS-B who were randomised to placebo but received treatment with tafamidis in the clinical trial, which was permitted in the trial design.

The PBAC considered this analysis had inherent uncertainties arising from its non-randomised nature and small sample sizes (discussed further in paragraphs 6.11, 6.22 and 6.39).

7.10 Based on the available evidence, the PBAC accepted vutrisiran is an effective therapy for the treatment of ATTR-CM, and noted the results of the stabilised IPTW did not find statistically significant differences between vutrisiran and tafamidis for the composite outcome of all-cause mortality and recurrent cardiovascular events (HR 0.83, 95% CI 0.54, 1.29) or for either of the component outcomes. However, as described in the paragraph above, the PBAC considered the stabilised IPTW to have inherent uncertainties and additionally noting the wide 95% confidence intervals, considered the claim of non-inferior comparative effectiveness based on the IPTW analysis alone to be uncertain. The PBAC noted the results of the MAIC analyses provided in the pre-PBAC Response were generally consistent with the results of the IPTW analysis. Taking into account the totality of evidence for vutrisiran and tafamidis in their respective clinical trials, the stabilised IPTW and MAIC analyses, the PBAC considered that it was reasonable to conclude that vutrisiran and tafamidis are associated with non-inferior comparative effectiveness in ATTR-CM in patients with NYHA Class I and II disease.

7.11 With respect to the evidence for the NYHA Class III with NAC stage 1 or 2 population (a subgroup of patients in the HELIOS-B trial), the PBAC noted the evidence was limited by the small sample size in the IPTW population and considered the evidence of benefit to be uncertain, noting that subgroup analyses showed wide confidence intervals.

7.12 The PBAC noted the claim of non-inferior comparative safety was informed only by a naïve side-by-side comparison of adverse events from the HELIOS-B and ATTR-ACT trials, as well as the stabilised IPTW populations. The Committee noted most outcomes had similar proportions experiencing adverse events of various types and severity, with tafamidis having numerically worse results for some outcomes in both the HELIOS-B tafamidis subgroup and the ATTR-ACT trial. Overall, the PBAC was satisfied that the claim of non-inferior comparative safety was adequately supported in ATTR-CM in patients with NYHA Class I and II disease.

7.13 The PBAC considered the cost minimisation approach (CMA) based on 12 months of treatment presented in the submission to be generally appropriate for patients with NYHA Class I and II disease, however considered that the following changes were required:

1) The effective price for tafamidis should be used, noting this was currently unknown by the sponsor. The PBAC noted that the recommended listing for vutrisiran was based on cost minimisation approach versus tafamidis, and there should be no additional cost per patient for vutrisiran compared with tafamidis.

2) The compliance modifiers should be removed and therefore 100% compliance should be assumed for both treatments. The PBAC considered that an assumption of lower compliance for vutrisiran was unlikely given the recommended administration

schedule for vutrisiran is SC injection once every 3 months compared to daily oral dosing for tafamidis.

3) The dosing interval for vutrisiran should reflect the interval in HELIOS-B as this was the clinical evidence supporting the claim of non-inferiority. The PBAC noted the dosing interval in HELIOS-B was 84 ± 7 days, which would equate to a range between 77 days and 91 days for vutrisiran).

4) The cost for administration should be informed by MBS item 116, consistent with the MBS item accepted for the vutrisiran listing for hATTR-PN. The PBAC considered that use of MBS item 3 (GP attendance) would underestimate the cost of administration of vutrisiran. The proportion of doses that would be administered via caregiver/patient was unknown, and therefore did not provide a basis for estimating a lower cost of administration.

7.14 The PBAC noted the CMA did not consider discontinuations, however considered these would be difficult to account for because the trial durations were different and discontinuations were only reported at 30 months for tafamidis and 36 months for vutrisiran. Overall, the PBAC acknowledged the uncertainty of attempting to transform a single whole-trial discontinuation figure to a rate that could be applied over the time horizon of the CMA and considered it was reasonable to not account for discontinuations in the CMA.

7.15 The PBAC noted that the recommended listing for vutrisiran was based on cost minimisation approach versus tafamidis and considered the impact of the proposed vutrisiran listing should be cost neutral.

7.16 The PBAC considered it would be appropriate for vutrisiran to join the tafamidis RSA, noting the submission assumed that 100% of vutrisiran use would replace tafamidis for patients with NYHA Class I and II disease.

7.17 The PBAC advised that vutrisiran is not suitable for inclusion in the PBS medicines for prescribing by nurse practitioners within collaborative arrangements.

7.18 The PBAC advised that vutrisiran should not be exempt from the Early Supply Rule.

7.19 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because vutrisiran is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over tafamidis, or not expected to address a high and urgent unmet clinical need given the presence of an alternative therapy, the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were not met.

7.20 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
VUTRISIRAN					
vutrisiran 25 mg/0.5 mL injection, 0.5 mL syringe	NEW	1	1	1	Amvuttra
Restriction Summary [new] / Treatment of Concept: [new]					
Concept ID (for internal Dept. use)	**Category / Program:** ☒ GENERAL - General Schedule (Code GE)				
	Prescriber type: ☒Medical Practitioners				
	Restriction type: ☒Authority Required (FULL assessment) in writing only via post/HPOS upload)				
Prescribing rule	**Administrative Advice:** No increase in the maximum quantity or number of units may be authorised.				
	Administrative Advice: No increase in the maximum number of repeats may be authorised.				
	Administrative Advice: Special Pricing Arrangements apply.				
	Indication: Transthyretin amyloid cardiomyopathy				
	Treatment Phase: First PBS-subsidised prescription for this drug				
	Clinical criteria				
	The treatment must be the sole PBS-subsidised disease modifying therapy for this condition				
	AND				
	Clinical criteria:				
	The condition must have documented evidence of transthyretin precursor protein present				
	AND				
	Clinical criteria:				
	Patient must have experienced at least one episode of hospitalisation that was a direct result of heart failure; or				
	Patient must have clinical evidence of heart failure without hospitalisation that required treatment with a diuretic for improvement				
	AND				
	Clinical criteria:				
	Patient must have/have had New York Heart Association class I heart failure at the time of commencing this drug; or				
	Patient must have/have had New York Heart Association class II heart failure at the time of commencing this drug,				
	AND				
	Clinical criteria:				
	Patient must have an end-diastolic interventricular septal wall thickness of at least 12 mm on imaging				
	AND				
	Clinical criteria:				
	Patient must have an estimated glomerular filtration rate (eGFR) of at least 30 mL/minute/1.73m^2				
	Treatment criteria:				
	Must be treated by a medical practitioner who is any of the following: (i) a cardiologist, (ii) a consultant physician with experience in the management of amyloid disorders; this authority application must be sought by the same medical practitioner providing treatment				

	Prescribing Instructions: The authority application must be made via the Online PBS Authorities System (see www.servicesaustralia.gov.au/hpos) or in writing via HPOS form upload or mail and must include: (a) details of the proposed prescription; and (b) a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice).
	Prescribing Instructions: Evidence of clinical findings to establish the diagnosis: In this authority application, confirm that there is documented evidence of transthyretin precursor protein through either (1) alone, or, both (2) and (3), from the list below: Confirm the following has been completed: (1) amyloid expert centre histology findings derived via immunohistochemistry or mass spectrometry; OR (2) bone scintigraphy with grade 2-3 finding AND (3) Confirm that there are negative results for monoclonal protein on each of the following three tests: (a) serum immunofixation (also known as protein electrophoresis) (b) urine immunofixation (c) serum free light chains blood test State which of (1) to (3) above has been completed, as well as the: (i) date of the finding, (ii) imaging/pathology report number/code that links the finding to the patient, (iii) name of the amyloid expert centre in this authority application (if applicable). For end-diastolic interventricular septal wall thickness (at least 12 mm), confirm that: (i) imaging (echocardiogram or magnetic resonance imaging) has been undertaken; and (ii) that the imaging report is stored in the patient's medical records. State the date that the imaging was performed and the thickness (in mm) in this authority application.
	Prescribing Instructions: Where this authority application is to transition a patient from non-PBS-subsidised to PBS-subsidised supply (i.e. a 'grandfathered' patient), confirm the following: (i) the patient's heart failure has not worsened to persistent New York Heart Association Class III/IV heart failure while taking this drug.
	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

	Administrative Advice: The Australian Amyloid Network provides a list of clinic centres that manage amyloidosis. It also provides a list of Australian anatomical pathology laboratories to be contacted for tissue review and immunohistochemistry for amyloid typing. For the purposes of this restriction, these providers are considered to be amyloid expert centres.
Restriction Summary [new] / Treatment of Concept: [new]	
Concept ID (for internal Dept. use)	**Category / Program:** ☒ GENERAL - General Schedule (Code GE)
	Prescriber type: ☒Medical Practitioners
	Restriction type: ☒Authority Required (immediate assessment)
	Indication: Transthyretin amyloid cardiomyopathy
	Treatment Phase: Second and subsequent PBS-subsidised prescriptions for this drug
	Clinical criteria:
	Patient must have previously received PBS-subsidised treatment with this drug for this condition
	AND
	Clinical criteria:
	The treatment must be the sole PBS-subsidised disease-modifying therapy for this condition
	AND
	Clinical criteria:
	Patient must have an estimated glomerular filtration rate (eGFR) of at least 30 mL/minute/1.73 m^2
	AND
	Clinical criteria:
	The treatment must be ceased where the patient's heart failure has worsened to persistent New York Heart Association (NYHA) Class III/IV heart failure,
	AND
	Clinical criteria:
	The treatment must be ceased where the patient has received any of: (i) a heart transplant, (ii) a liver transplant, (iii) an implanted ventricular assist device
	Treatment criteria:
	Must be treated by a medical practitioner who is any of the following: (i) a cardiologist, (ii) a consultant physician with experience in the management of amyloid disorders; this authority application must be sought by the same medical practitioner providing treatment
	Prescribing Instructions: Confirm whether heart failure has worsened to NYHA Class III/IV since the last authority application (yes/no). If 'no', continued PBS subsidy is available. If 'yes', continued PBS subsidy is available, but the prescriber must undertake a review of the patient within 3 months to determine whether the worsening heart failure was transient or persistent. Where this subsequent clinical review finds that the heart failure persists as NYHA Class III/IV heart failure despite active treatment with this drug, then PBS subsidy is not available.
	Prescribing Instructions: If heart failure has worsened to NYHA Class III/IV since the last authority application, no repeat prescriptions must be prescribed.
	Administrative Advice: Applications for authorisation under this restriction may be made in 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).

8.2 Flow-on changes to PBS-subsidised tafamidis listed for ATTR-CM (PBS item: 14100D) to prevent combination treatment of tafamidis and vutrisiran.

Addition of the following clinical criterion to PBS-subsidised tafamidis listed for ATTR-CM (PBS item: 14100D)

	Clinical criteria:
	The treatment must be the sole PBS-subsidised disease-modifying therapy for this condition

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

9 Context for Decision

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

10 Sponsor's Comment

The sponsor had no comment.