

**5.24 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 Category 2 submission for vutrisiran requested a General Schedule, Authority Required (Written) listing for the treatment of hereditary transthyretin mediated (hATTR) amyloidosis in adult patients with stage 1 or stage 2 polyneuropathy, defined by Familial Amyloid Neuropathy (FAP) stage.
- 1.2 Listing was requested on the basis of a cost-minimisation approach versus patisiran.

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

Component	Description
Population	Adult patients with hATTR amyloidosis and stage 1 or 2 polyneuropathy, defined by FAP stage.
Intervention	Vutrisiran (25 mg in 0.5 mL prefilled syringe) 3 monthly by subcutaneous injection.
Comparator	Patisiran (0.3 mg/kg solution for injection) 3 weekly by intravenous infusion.
Outcomes	Changes in neurological impairment (mNIS+7 composite score), patient-reported HRQoL (Norfolk QoL-DN), polyneuropathy progression (PND score), ambulatory ability (10-MWT), ability to perform everyday activities (R-ODS), nutritional status (mBMI), health related quality of life (EQ-5D), serum TTR, and adverse events.
Clinical claim	Vutrisiran has a comparable efficacy profile and comparable/superior safety profile compared to patisiran, with less burdensome administration.

Source: Table 1.1, p13 of the submission.

Abbreviations: 10-MWT, 10-metre walk test; FAP, familial amyloid polyneuropathy; hATTR, hereditary transthyretin mediated amyloidosis; HRQoL, health related quality of life; mBMI, modified body mass index; PND, polyneuropathy disability; Norfolk QoL-DN, Norfolk Quality of Life–Diabetic Neuropathy; R-ODS, Rasch-built overall disability score; TTR, transthyretin.

2 Background

Registration status

- 2.1 Vutrisiran 25 mg every 3 months was registered by the TGA on 21 June 2024, for the treatment of hATTR amyloidosis in adult patients with stage 1 or stage 2 polyneuropathy.

3 Requested listing

- 3.1 Suggested additions are in italics and deletions are in strikethrough.

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MEDICINAL PRODUCT medicinal product pack	Dispensed Price for Max. Qty	Max. qty packs	Max. qty units	No. of Rpts	Available brands
VUTRISIRAN					
Vutrisiran, prefilled syringe for subcutaneous injection (25 mg in 0.5 mL)	General Schedule as requested by submission: \$ (published) \$ (effective)	1	1	1	Amvuttra

Category / Program: General Schedule Section 100 – Highly Specialised Drugs Program – Public and Private Hospitals
Prescriber type: Medical Practitioners
Restriction type: Authority Required (in writing only via post/HPOS upload)
Condition: Hereditary transthyretin amyloidosis
Indication: Hereditary transthyretin amyloidosis
Treatment Phase: Initial treatment
Population criteria: Patient must have either (i) stage 1 polyneuropathy, (ii) stage 2 polyneuropathy
Clinical criteria: Patient must not have previously received PBS-subsidised treatment with this drug for this PBS indication
AND
Clinical criteria: Patient must be at least 18 years of age
AND
Clinical criteria: The condition must be hereditary transthyretin amyloidosis confirmed by genetic testing
AND
Clinical criteria: Patient must have a Polyneuropathy Disability (PND) score description of either I, II, IIIA, IIIB, OR Patient must have a Familial Amyloid Polyneuropathy (FAP) stage description of 1 or 2
Clinical criteria: Patient must not have previously undergone a liver transplant
AND
Clinical criteria: Patient must not exhibit heart failure symptoms (defined as New York Heart Association [NYHA] class III or IV)
Treatment criteria: Must be treated by a consultant with experience in the management of amyloid disorders or in consultation with a consultant with experience in the management of amyloid disorders
Vutrisiran is to be used <i>Patient must be undergoing treatment with this drug as a monotherapy (i.e. not in combination with any other disease modifying medicines for amyloidosis disorders)</i>
Prescriber type: Medical Practitioners
Restriction type: Authority Required (in writing only via post/HPOS upload)
Condition: Hereditary transthyretin amyloidosis
Indication: Hereditary transthyretin amyloidosis
Treatment Phase: Continuing treatment
Population criteria: Patient must have previously received PBS-subsidised treatment with this drug for this condition
Clinical criteria:

Patient must continue to demonstrate clinical benefit
AND
Clinical criteria:
Patient must not be permanently bedridden, OR
Patient must not be receiving end-of-life care
Prescriber type: Medical Practitioners
Restriction type: Authority Required (in writing only via post/HPOS upload)
Condition: Hereditary transthyretin amyloidosis
Indication: Hereditary transthyretin amyloidosis
Treatment Phase: Grandfather arrangements
Population criteria:
Patient must have received treatment with this drug for this condition prior to [PBS listing date]
Clinical criteria:
Patient must continue to demonstrate clinical benefit
AND
Clinical criteria:
<i>Patient must have had a Polyneuropathy Disability (PND) score description of either I, II, IIIA, IIIB prior to commencing non-PBS subsidised therapy; OR</i>
<i>Patient must have had a Familial Amyloid Polyneuropathy (FAP) stage description of 1 or 2 prior to commencing non-PBS subsidised therapy.</i>
AND
Clinical criteria:
<i>Patient must not have previously undergone a liver transplant</i>
AND
Clinical criteria:
<i>Patient must not have exhibited heart failure symptoms (defined as New York Heart Association [NYHA] class III or IV) prior to commencing non-PBS subsidised therapy.</i>
AND
Clinical criteria:
Patient must not be permanently bedridden, OR
Patient must not be receiving end-of-life care

- 3.2 The submission proposed an effective vutrisiran AEMP of \$ [REDACTED], and a published AEMP of \$ [REDACTED], per prefilled syringe (25 mg vutrisiran).
- 3.3 The requested listing is narrower than the TGA registered indication, limiting initial eligibility to adult patients with FAP Stage 1 or Stage 2 polyneuropathy, who have not undergone a liver transplant, do not exhibit heart failure symptoms (New York Heart Association Class III or Class IV) and have not previously received treatment with vutrisiran. Under the proposed restriction, patients progressing to PND IV may continue PBS subsidised treatment with vutrisiran so long as they continue to experience clinical benefit, unless the patient is permanently bedridden or receiving end-of-life care.
- 3.4 The proposed listing is based on the PBS listing for patisiran, but requests a Section 85 General Schedule listing, instead of a Section 100 (Highly Specialised Drugs Program) listing. Given vutrisiran will most likely be administered by health care professionals

in hospitals or outpatient clinics, a Section 100 listing may be more appropriate. The Pre-Sub-Committee Response (PSCR,) maintained that a General Schedule listing for vutrisiran was appropriate and that, although the patient may be under follow-up with a specialist, allowing vutrisiran to be dispensed through community pharmacies broadly would improve patients' access. The PSCR and Pre-PBAC Response also stated that the sponsor is open to a Section 100 (Highly Specialised Drugs Program) listing in the Community Access schedule, if considered appropriate by the PBAC. The PBAC advised that a Section 100 (Highly Specialised Drugs Program - Public and Private Hospitals) listing was appropriate (paragraph 7.1). It was noted that, as a Complex Authority Required (CAR) medicine, the dispensing of vutrisiran would be permitted in community pharmacies. The Services Australia website provides details regarding which PBS Approved Suppliers can dispense HSD items¹.

- 3.5 The requested restriction is broadly consistent with the inclusion criteria of the key HELIOS-A study. However, the HELIOS-A study also excluded patients with a history of type 1 diabetes, type 2 diabetes (≥ 5 years), acute coronary syndrome, uncontrolled cardiac arrhythmias or unstable angina, and there was no evidence presented supporting the use of vutrisiran in these populations.

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

4 Population and disease

- 4.1 hATTR is an inherited, autosomal dominant, progressive, and debilitating disease caused by the accumulation of both hereditary (or variant) and wild-type amyloid fibrils. It is a multisystem disease with heterogeneous clinical presentations including sensory, motor, and autonomic functions (e.g., bowel dysfunction, urinary incontinence, sexual dysfunction, orthostatic intolerance), primarily characterised by polyneuropathy and/or cardiomyopathy, with the potential involvement of other organ systems (e.g. gastrointestinal).
- 4.2 hATTR amyloidosis with polyneuropathy is an ultra-rare variant associated with significant morbidity, rapid disease progression, and premature death. The related pathophysiology may initially be a small-fibre neuropathy, causing sensory loss and pain in the toes and feet, progressing to large-fibre neuropathy associated with constipation alternating with diarrhoea, nausea and vomiting, orthostatic hypotension, sexual dysfunction, increasing weakness, gait dysfunction, and eventually loss of ambulation (Kittleson 2023).
- 4.3 The prevalence of hATTR amyloidosis with polyneuropathy has been estimated at approximately 10,000 affected individuals worldwide. Based on 2014 international

¹ <https://www.servicesaustralia.gov.au/dispensing-highly-specialised-drugs-hsd?context=20#accordion2>

data, Schmidt et al. (2018) determined low (0.32 per million), intermediate (1.48 per million), and high (7.52 per million) prevalence estimates based on available prevalence data from countries with directly estimable affected populations, where hATTR amyloidosis with polyneuropathy is not endemic. Extrapolated to the Australian setting, this suggested a range of potential prevalent populations of approximately 9 (low), 41 (intermediate), or 210 (high) in 2025.

- 4.4 Vutrisiran is a disease-modifying double-stranded small interfering RNA (siRNA) medicine, that specifically targets the expression of variant and wild-type TTR messenger RNA (mRNA) in the liver using the endogenous RNAi pathway, decreasing the synthesis of both variant and wild-type TTR proteins. Vutrisiran is formulated as a trivalent N-acetylgalactosamine conjugate with a strong affinity for asialoglycoprotein receptors on hepatic cell membranes, using enhanced stabilisation chemistry.
- 4.5 Vutrisiran (25 mg in 0.5 mL pre-filled syringe) is administered once every 3 months by subcutaneous injection.
- 4.6 The submission positioned vutrisiran as an alternative to patisiran as first-line treatment for diagnosed hATTR amyloidosis with polyneuropathy, in combination with best supportive care. The submission assumed that vutrisiran will rapidly replace patisiran as the preferred treatment for all eligible patients, due to the patient burden associated with patisiran administration, pre-medication, and infusion related adverse events.

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

5 Comparator

- 5.1 The submission nominated patisiran as the main comparator. The main argument provided in support of this nomination was that patisiran is the only PBS recommended therapy for hATTR amyloidosis with polyneuropathy, and the medicine most likely to be replaced by vutrisiran in clinical practice. The ESC agreed with the evaluation that patisiran is the appropriate main comparator.
- 5.2 The submission noted that patisiran was the first therapy approved by the TGA for the treatment of hATTR amyloidosis with polyneuropathy. Patisiran was listed on the PBS on 1 August 2024 for that indication.
- 5.3 Patisiran is administered once every 3 weeks by intravenous infusion (3 mg/kg up to maximum of 30 mg for patients ≥ 100 kg, over approximately 80 minutes), and requires premedication with corticosteroids, antihistamines and oral paracetamol, to reduce the risk of infusion related reactions.
- 5.4 The submission noted that tafamidis, currently listed on the PBS for the treatment of transthyretin amyloid cardiomyopathy, is not a near market comparator, as it is not approved for use in patients with hATTR amyloidosis with polyneuropathy in the Australian setting. Both tafamidis and diflunisal have been shown to be effective in slowing the progression of hATTR with polyneuropathy (Kittleson 2023), and tafamidis

has been approved by the European Medicines Agency (EMA) for the treatment of transthyretin amyloidosis in adult patients with stage 1 symptomatic polyneuropathy to delay peripheral neurologic impairment. In addition, the FDA has approved inotersen, as well as patisiran and vutrisiran, for the treatment of hATTR polyneuropathy (Kittleson 2023).

- 5.5 Both vutrisiran and patisiran are given in combination with best supportive care and must be administered by health professionals. Best supportive care was not defined in the submission but is assumed to be similar for both agents. Given that treatment with vutrisiran or patisiran reduces serum TTR protein and may decrease serum vitamin A, vitamin A supplementation is recommended to be administered concurrently with both treatments, to reduce the potential risk of ocular toxicity.

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

6 Consideration of the evidence

Sponsor hearing

- 6.1 There was no hearing for this item.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from individuals (12) and the Leukaemia Foundation. The Committee noted the input from individuals described the burden of living with hATTR amyloidosis and the effectiveness of vutrisiran (as well as patisiran) at improving the symptoms of their condition and slowing the progression of disease. The input also outlined the advantages to patients of having a treatment delivered as a subcutaneous injection every 3 months, as opposed to the requirements to attend an infusion centre to receive patisiran once every 3 weeks, in terms of improved ability to work and travel and an increased sense of freedom.
- 6.3 The Committee also recognised the input from the Leukaemia Foundation which discussed the burden of living with hATTR amyloidosis, and highlighted the convenience of vutrisiran with its less frequent dosing requirements.

Clinical studies

- 6.4 The submission was based on one randomised open label study of vutrisiran (HELIOS-A) with a vutrisiran treatment arm (n=122) and a small patisiran reference arm (n=42). This also included a pre-specified comparison with an external placebo arm from the APOLLO study. APOLLO was a randomised double-blind study of patisiran (n=148) versus placebo (n=77), previously considered by the PBAC at the July 2023, September 2023 and December 2023 meetings (Patisiran Public Summary Document (PSD), July 2023 PBAC meeting, September 2023, December 2023 addenda).

- 6.5 In addition, the submission presented comparisons of the vutrisiran and patisiran arms of the HELIOS-A study (a post hoc comparison of the primary and key secondary outcomes; and a prespecified noninferiority analysis in the secondary outcome of change in serum TTR).
- 6.6 A supportive network meta-analysis based on the HELIOS-A and APOLLO studies was also presented.
- 6.7 Details of the studies presented in the submission are provided in Table 2.

Table 2: Studies presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Vutrisiran		
HELIOS-A	A phase 3 global, randomised, open-label study to evaluate the efficacy and safety of ALN-TTRSC02 (vutrisiran) in patients with hereditary transthyretin amyloidosis (hATTR amyloidosis).	Clinical Study Report: 23 March 2021.
	A phase 3 global, randomised, open-label study to evaluate the efficacy and safety of ALN-TTRSC02 in patients with hereditary transthyretin amyloidosis (hATTR amyloidosis): 18 month analysis.	Clinical Study Report: 10 January 2022.
	Adams D, Tournev IL, Taylor MS, et al. Efficacy and safety of vutrisiran for patients with hereditary transthyretin-mediated amyloidosis with polyneuropathy: a randomised clinical trial.	Amyloid. 2023, 30(1):1-9.
	Polydefkis M, Bircklein F, Sekijima Y, et al. Comparison of efficacy outcomes with vutrisiran vs patisiran in hATTR amyloidosis with polyneuropathy: post-hoc analysis of the HELIOS-A study. Presented at the 75th Annual Meeting of the American Academy of Neurology (AAN), Boston, 22–27 April 2023.	Neurology. 2023, 100(17).
	HELIOS-A extension phase: Obici L, Polydefkis M, Gonzalez-Duarte A, et al. HELIOS-A: 9-month results from the randomized treatment extension period of vutrisiran in patients with hereditary transthyretin-mediated amyloidosis with polyneuropathy. Abstract and Poster [Presented at the 13th Annual Meeting of the Association for the study of the Peripheral Nervous System (ASNP), Naples, Italy, 25–27, May].	J Peripher Nerv Syst. 2023;28:S40.
Patisiran		
APOLLO	A phase 3 multicenter, multinational, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of patisiran (ALN-TTR02) in transthyretin (TTR)- mediated polyneuropathy (Familial Amyloidotic Polyneuropathy-FAP).	Clinical Study Report: 20 November 2017.
	Adams D, Gonzalez-Duarte A, O’Riordan WD, et al. Patisiran, an RNAi therapeutic, for hereditary transthyretin amyloidosis.	New England Journal of Medicine. 2018, 379(1):11-21.

Source: Table 2.3, p32 of the submission.

- 6.8 The key features of the studies are summarised in Table 3.

Table 3: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes
Vutrisiran versus patisiran					
HELIOS-A	164	Randomised, open-label, active control (reference) multicentre trial, 18 months	High	18-85 years, hATTR amyloidosis, NIS 5-130, PND \leq IIIB, KPS \geq 60	Primary: change in mNIS+7 Secondary: Norfolk QoL-DN, R-ODS, 10-MWT, mBMI, Exploratory: change in PND, serum TTR reduction, EQ-5D-5L
Patisiran versus placebo					
APOLLO	225	Randomised, double blind, placebo controlled multicentre trial, 18 months	Low	18-85 years, hATTR amyloidosis with polyneuropathy, NIS of 5-130, PND of \leq IIIB, KPS \geq 60	Primary: change in mNIS+7 Secondary: Norfolk QoL-DN, R-ODS, 10-MWT, mBMI, Exploratory: change in PND score, serum TTR reduction, EQ-5D-5L

Source: Compiled during the evaluation from Section 2 of the submission.

Abbreviations: 10-MWT, 10 metre walk test; CI, confidence interval; hATTR, hereditary transthyretin mediated amyloidosis; KPS, Karnofsky performance status; mBMI, modified body mass index; mNIS+7, modified neuropathy impairment score +7; NIS, Neuropathy Impairment Score; PND, polyneuropathy disability; QoL-DN, quality of life-diabetic neuropathy; R-ODS, Rasch-built Overall Disability Score.

- 6.9 The HELIOS-A study is an ongoing randomised open label study investigating the efficacy and safety of vutrisiran in the treatment of adults with hATTR amyloidosis with polyneuropathy, over 18 months of treatment. Patients were randomised to treatment with vutrisiran or patisiran in a 3:1 ratio, stratified by TTR genotype (V30m versus other mutation), and baseline Neuropathy Impairment Score (<50 versus \geq 50). The HELIOS-A study design, inclusion criteria and outcomes were based on the APOLLO study, and the primary analysis of the HELIOS-A study was a pre-specified comparison between the HELIOS vutrisiran treatment arm, and the external placebo arm of the APOLLO study (historical placebo).
- 6.10 The risk of bias in the HELIOS-A study was high, given the open label study design. The risk of bias in the APOLLO study was low, notwithstanding a risk of attrition bias due to a larger proportion of patients in the placebo group withdrawing from the study, and a related potential for functional unblinding of treatment groups. The pre-specified use of the APOLLO placebo arm in the HELIOS-A primary analysis, introduced a substantial risk of attrition bias in the primary outcome, given substantial differences in treatment and/or study discontinuation between studies (HELIOS-A vutrisiran arm 4.1%; APOLLO placebo arm 37.7%). The Pre-PBAC Response argued that TTR is an objective laboratory measure that is not subject to interpretation by investigators, nor influenced by participant knowledge of treatment assignment.
- 6.11 The dosing of vutrisiran and patisiran in HELIOS-A were consistent with the Product Information recommendations for each agent. In HELIOS-A, administration of vutrisiran and patisiran was permitted outside the study centre and in the patient's home, by a home healthcare professional or caregiver, or by self-administration (vutrisiran only) after appropriate training and one or more administrations at a study centre. The vutrisiran and patisiran product information documents specify that both agents must be administered by a healthcare professional.

- 6.12 All randomised patients in the HELIOS-A and APOLLO studies received an intervention, with small proportions of patients in the vutrisiran (4.1%) and patisiran (HELIOS-A 9.5%; APOLLO 7.4%) treatment arms discontinuing treatment and/or withdrawing from the studies compared to the APOLLO placebo arm (37.7%). Treatment discontinuation in the HELIOS-A study included 2 patients (one in each treatment arm) who discontinued treatment due to the impact of COVID-19, and larger proportions of patients treated with patisiran (42.9%) who experienced delayed or missed doses due to COVID-19, compared to vutrisiran (13.9%). The most common reason for discontinuing treatment in the active treatment arms was death (HELIOS-A vutrisiran 1.6%; patisiran 7.1%; APOLLO patisiran 3.4%). Differences in the proportions of deaths between arms were not considered important by the evaluation, given the small size of the HELIOS-A patisiran arm.
- 6.13 Baseline patient demographic characteristics were broadly similar between the HELIOS-A and APOLLO studies, but disease characteristics varied between studies. Patients in the HELIOS-A study generally had less severely impacted function compared to the APOLLO study, with larger proportions of patients reporting baseline FAP stage 1 (FAP 1 in HELIOS-A vutrisiran 70%, patisiran 74%; APOLLO patisiran 45%), and PND Stage 1 or 2 (PND 1 or 2 in HELIOS-A vutrisiran 77%, patisiran 77%; APOLLO patisiran 53%).
- 6.14 There were substantial differences between the HELIOS-A study vutrisiran treatment arm and the APOLLO placebo arm used as the historical control, in terms of mean age (HELIOS-A vutrisiran 57.8 years; APOLLO placebo 62.2 years), male sex (HELIOS-A vutrisiran 65%; APOLLO placebo 75%), Asian race (HELIOS-A vutrisiran 17%; APOLLO placebo 33%), TTR genotype V30M (HELIOS-A vutrisiran 44%; APOLLO placebo 52%), prior use of tetramer stabilisers (HELIOS-A vutrisiran 62%; APOLLO placebo 53%), FAP Stage 1 (HELIOS-A vutrisiran 70%; APOLLO placebo 48%), PND score I or II (HELIOS-A vutrisiran 77%; APOLLO placebo 56%), and NYHA Class 1 or 2 (HELIOS-A vutrisiran 65%; APOLLO placebo 52%).
- 6.15 In HELIOS-A, a prespecified noninferiority analysis of vutrisiran versus patisiran was conducted for percent serum TTR reduction from baseline (lower limit of the 95% confidence interval for the median treatment difference in TTR percent reduction greater than -10%). Noninferiority margins were not nominated for other outcomes.
- 6.16 The PSCR argued that hATTR amyloidosis is a very rare condition and consideration should be given to the data that can reasonably be collected in this cohort, and although the results of the HELIOS-A study may not have demonstrated statistical significance on all outcomes, the results are consistent and numerically tend to favour vutrisiran over patisiran. The PSCR also reiterated HELIOS-A was designed and powered to assess within-trial non-inferiority of vutrisiran and patisiran in terms of change in serum TTR as a pre-specified secondary endpoint. The PSCR highlighted that to power a formal non-inferiority study based on mNIS+7 would have required a sample size of approximately 400 patients, which would have been difficult to recruit given the rarity of the condition, and that a substantial number of patients may have

already participated in trials for other candidate treatments. The ESC acknowledged these issues are genuine impediments to conducting a larger trial which could have more definitively established the comparative effectiveness of vutrisiran and patisiran on more patient-relevant outcomes, but considered the reliance on serum TTR as a surrogate marker to primarily support the clinical claim of non-inferior comparative effectiveness remained a source of uncertainty.

- 6.17 Patients completing the 18-month treatment phase of the HELIOS-A study, could continue into an 18-month treatment extension period (an ongoing observational study), and were re-randomised to treatment with vutrisiran 25 mg once every 3 months or vutrisiran 50 mg once every 6 months. Listing of the vutrisiran 50 mg once 6 monthly regimen was not requested in the submission. Limited results of the extension study were presented, based on a preliminary analysis at 9 months (poster/abstract only; Obici et al 2023). Results included a mix of patients continuing vutrisiran and switching to vutrisiran from patisiran, with unknown patient disposition on re-randomisation and uncertain duration of treatment with vutrisiran and respective dose regimens.

Comparative effectiveness

Vutrisiran versus placebo

- 6.18 Table 4 summarises the change from baseline to Month 18 in the HELIOS-A primary outcome of mNIS+7 (including subscales), comparing vutrisiran with an external placebo arm from the APOLLO study.

Table 4: Change in mNIS+7 and component subscales from baseline to Month 18 (external placebo; mITT)

Outcomes	HELIOS-A vutrisiran (n=122)	APOLLO external placebo (n=77)	HELIOS-A Vutrisiran (n=112)	APOLLO external placebo (n=51)	Difference LS mean change (95% CI)
	Baseline mean (SD)		LS mean change from baseline (SEM)		
mNIS+7 (total score) ^a	60.57 (35.99)	74.61 (37.04)	-0.46 (1.60)	28.09 (2.28)	-28.55 (-34.00, -23.10)
NIS-weakness	20.9 (19.7)	29.0 (22.9)	0.89 (1.13)	19.30 (1.61)	-18.4 (-22.3, -14.6)
NIS-reflexes	10.3 (6.5)	12.8 (5.9)	-0.02 (0.32)	1.84 (0.46)	-1.86 (-2.96, -0.77)
QST	23.0 (17.5)	24.8 (15.3)	-1.8 (1.1)	6.5 (1.6)	-8.27 (-12.00, -4.54)
Σ5 NCS	5.98 (3.47)	7.43 (2.24)	0.05 (0.11)	1.14 (0.15)	-1.09 (-1.45, -0.72)
PBP	0.36 (0.60)	0.61 (0.74)	0.0 (0.06)	0.18 (0.09)	-0.18 (-0.38, 0.03)

Source: Table 2.14, p50 of the submission.

Abbreviations: Σ5 NCS, nerve conduction studies; CI, confidence interval; LS, least squares; mITT, modified intention-to-treat; mNIS+7, modified neuropathy impairment score +7; Pbo, placebo; PBP, postural blood pressure; QST, quantitative sensory testing; SD, standard deviation; SEM, standard error mean.

^a Lower scores indicate less impairment/fewer symptoms.

Note: Statistically significant results in bold.

- 6.19 In HELIOS-A, change from baseline to Month 18 in mNIS+7 showed a statistically significant difference between vutrisiran and the APOLLO study placebo arm. The difference between treatment arms exceeded the nominated MCID of 2 points, and the MCID of 12.2 points reported in Yarlas (2022), a study that derived MCID thresholds using an anchor-based approach based on data from the inotersen NEURO-

TTR trial. The least squares mean difference in mNIS+7 score favouring vutrisiran in the HELIOS-A study (-28.55), was similar to that reported for patisiran versus placebo in the APOLLO study (-33.99).

6.20 All mNIS+7 subscale components showed statistically significant differences favouring vutrisiran compared to the APOLLO study placebo arm, excepting the postural blood pressure scale which failed to demonstrate statistical significance. Similarly, in the APOLLO study, all mNIS+7 subscale components showed statistically significant differences favouring patisiran compared to placebo, excepting the NIS-reflexes scale which failed to demonstrate statistical significance.

6.21 Table 5 summarises the change from baseline to Month 9 and Month 18 in the HELIOS-A study secondary outcomes, for vutrisiran and the APOLLO study placebo arm.

Table 5: HELIOS-A primary and secondary outcomes at Month 9 and Month 18 (external placebo; mITT)

Outcomes	HELIOS-A vutrisiran (n=122)	APOLLO external placebo (n=77)	HELIOS-A vutrisiran	APOLLO external placebo	Difference LS mean change (95% CI)
	Baseline mean (SD)		LS mean change from baseline (SEM)		
Change from baseline to Month 9 (interim)					
mNIS+7 (total score) ^a	60.6 (36.0)	74.6 (37.0)	n=116 -2.2 (1.4)	n=67 14.8 (2.0)	-17.0 (-21.8, -12.2)
Norfolk QoL-DN ^{a,c}	47.1 (26.3)	55.5 (24.3)	n=115 -3.3 (1.7)	n=65 12.9 (2.2)	-16.2 (-21.7, -10.8)
10-MWT ^{b,c} (m/sec)	1.01 (0.39)	0.79 (0.32)	n=115 0 (0.02)	n=68 -0.13 (0.03)	0.13 (0.07, 0.19)
Change from baseline to Month 18 (final)					
Norfolk QoL-DN ^{a,c}	47.1 (26.3)	55.5 (24.3)	n=111 -1.2 (1.8)	n=48 19.8 (2.6)	-21.0 (-27.1, -14.9)
10-MWT ^{b,c} (m/sec)	1.006 (0.393)	0.790 (0.319)	n=112 -0.024 (0.025)	n=55 -0.264 (0.036)	0.239 (0.154, 0.325)
R-ODS ^{b,c}	34.1 (11.0)	29.8 (10.8)	n=113 -1.5 (0.6)	n=54 -9.9 (0.8)	8.4 (6.5, 10.4)
mBMI ^{b,c} (g/L×kg/m ²)	1057.5 (234.0)	989.9 (214.2)	n=113 25.0 (9.5)	n=52 -115.7 (13.4)	140.7 (108.4, 172.9)

Source: Table 2.14, p50 of the submission.

Abbreviations: 10-MWT, 10 metre walk test; CI, confidence interval; LS, least squares; mBMI, modified body mass index; mITT, modified intention-to-treat; mNIS+7, modified neuropathy impairment score +7; QoL-DN, quality of life-diabetic neuropathy; R-ODS, Rasch-built Overall Disability Score; SD, standard deviation; SEM, standard error mean.

^a Lower scores indicate less impairment/fewer symptoms.

^b Higher values indicate less disability/less impairment, or better nutritional status. mBMI = albumin (g/L) x weight (kg) / height (m²).

^c Type I error control for secondary endpoints by hierarchical ordering procedure.

Note: Statistically significant results in bold.

6.22 In HELIOS-A, change from baseline to Month 9 in mNIS+7 showed a statistically significant difference between vutrisiran and the APOLLO study placebo arm, favouring vutrisiran. All secondary outcomes showed statistically significant differences favouring vutrisiran compared to the external placebo. Similarly, in APOLLO, all secondary outcomes showed statistically significant differences favouring patisiran compared to placebo.

- 6.23 The results of the change in EQ-5D-5L from baseline to Month 9 and Month 18, showed statistically significant benefits for patients treated with vutrisiran compared to the external placebo. The least squares mean difference in EQ-5D-5L index between vutrisiran and placebo from baseline to Month 18 (LS mean difference 0.19, 95% CI: 0.14, 0.23) was similar to that observed for patisiran versus placebo in the APOLLO study (LS mean difference 0.20, 95% CI: 0.15, 0.25).
- 6.24 Table 6 summarises the preliminary results of the primary and secondary outcomes in the HELIOS-A extension study, from the extension period baseline to 9 months.

Table 6: HELIOS-A extension primary and secondary outcomes from extension baseline to Month 9

Outcomes	Vutrisiran 25 mg (Q3M) (n=66)	Vutrisiran 50 mg (Q6M) (n=64)
	Mean change (SE)	
mNIS+7 (total score) ^a	-0.21 (1.82)	0.88 (1.64)
Norfolk QoL-DN ^a	1.1 (2.0)	4.5 (1.8)
10-MWT ^b (m/sec)	-0.061 (0.023)	-0.069 (0.022)
R-ODS ^b	-1.1 (0.5)	-1.7 (0.6)
mBMI ^b (g/L×kg/m ²)	8.5 (10.9)	-4.1 (9.7)

Source: Table 2, p50 Obici et al. (2023).

Abbreviations: 10-MWT, 10 metre walk test; CI, confidence interval; mBMI, modified body mass index; mNIS+7, modified neuropathy impairment score +7; QoL-DN, quality of life-diabetic neuropathy; R-ODS, Rasch-built Overall Disability Score; SE, standard error.

^a Lower scores indicate less impairment/fewer symptoms.

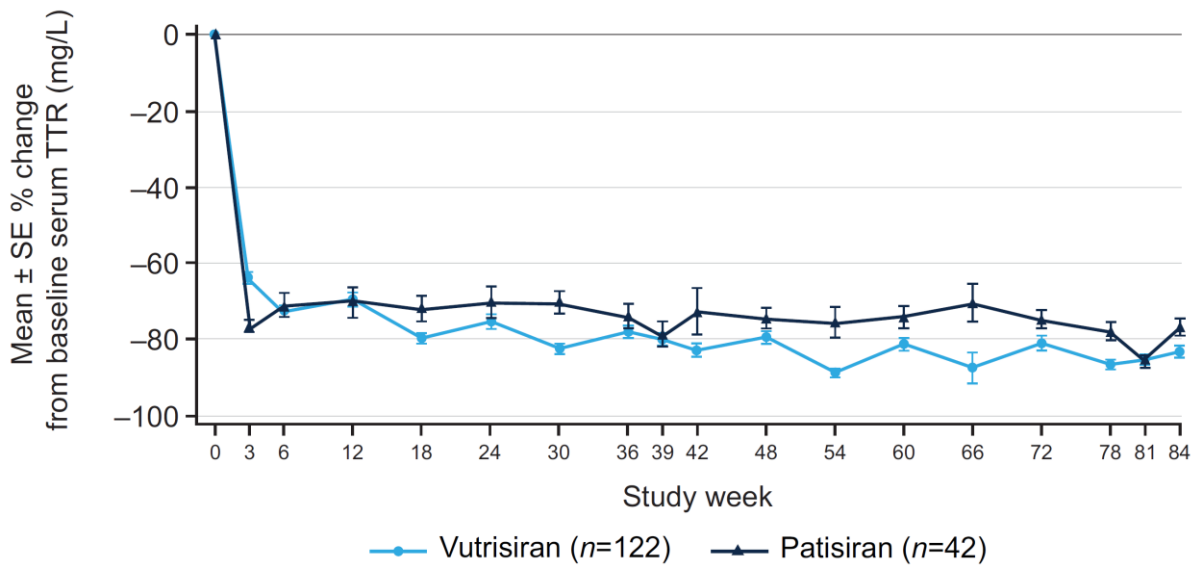
^b Higher values indicate less disability/less impairment, or better nutritional status. mBMI = albumin (g/L) x weight (kg) / height (m²).

- 6.25 Preliminary results of the HELIOS-A extension period at Month 9, showed similar changes in the primary and secondary outcomes for patients treated with vutrisiran 25 mg once every 3 months compared to vutrisiran 50 mg once every 6 months. The results of the HELIOS-A 18 month extension period at 9 months suggested that the benefits of treatment with vutrisiran may continue to be observed after 9 months of additional treatment. However, given that the preliminary results only reported change in outcomes from the extension baseline to 9 months comparing the efficacy and safety of vutrisiran dose regimens after re-randomisation and included a mix of patients continuing vutrisiran or switching to vutrisiran from patisiran, as well as the poor reporting of patient disposition on re-randomisation, the results should be considered with caution and are not comparable with other observed vutrisiran or patisiran outcomes.

Vutrisiran versus patisiran

- 6.26 Figure 1 below, summarises the results of the secondary outcome of percentage serum TTR reduction from baseline to Month 18, comparing the HELIOS-A vutrisiran arm and reference patisiran arm (noninferiority analysis) in the per protocol population (i.e. all patients with a TTR assessment at baseline and ≥1 trough TTR assessment between Months 6 and Month 18 that met the postbaseline TTR assessment requirements).

Figure 1: HELIOS-A percentage change in serum TTR to Month 18 (PP)



N evaluable																		
Vutrisiran (n=122)	122	114	109	119	106	117	92	118	115	56	116	42	118	15	118	100	114	98
Patisiran (n=42)	42	42	41	41	37	38	39	34	39	23	40	23	36	9	37	36	38	32

Source: Figure 2.6, p55 of the submission.

Abbreviations: PP, per protocol; SE, standard error; TTR, transthyretin.

- 6.27 Patients treated with vutrisiran and patisiran reported a rapid and sustained reduction in serum TTR levels over 18 months. Steady-state mean peak and trough serum TTR reductions from baseline for patients treated with vutrisiran were 87.6% and 81.0% respectively, with a less than 10% difference to steady-state mean peak and trough serum TTR reductions for patients treated with patisiran (86.0% and 74.7% respectively). The results met the prespecified threshold for statistical non-inferiority nominated in the submission.
- 6.28 Table 7 summarises the results of post hoc analyses comparing the HELIOS-A vutrisiran and reference patisiran arms, for the primary and key secondary outcomes.

Table 7: HELIOS-A post hoc comparison of vutrisiran vs patisiran (reference) for primary and key secondary outcomes at Month 18 (mITT)

Outcome	HELIOS-A				Difference LS mean change (95% CI)
	Vutrisiran (n=122)	Patisiran (n=42)	Vutrisiran	Patisiran	
	Baseline mean (SD)		LS mean change from baseline Month 18 (SEM)		
mNIS+7 (total score) ^a	60.57 (35.99)	74.61 (37.04)	0.06 (1.48)	1.53 (2.59)	-1.46 (-7.36, 4.43)
Norfolk QoL-DN ^a	47.1 (26.3)	55.5 (24.3)	-2.5 (1.8)	-0.8 (3.0)	-1.6 (-8.6, 5.4)
10-MWT ^b (m/sec)	1.01 (0.39)	1.01 (0.40)	-0.02 (0.03)	-0.05 (0.04)	0.034 (-0.064, 0.132)
R-ODS ^b	34.1 (11.0)	34.0 (10.4)	-0.2 (0.5)	-0.3 (0.9)	0.1 (-2.0, 2.2)
mBMI ^b (g/L×kg/m ²)	1057.4 (233.8)	1058.1 (228.8)	21.8 (9.2)	7.6 (15.8)	14.2 (-21.9, 50.3)

Source: Table 2.14, p50 of the submission.

Abbreviations: 10-MWT, 10 metre walk test; CI, confidence interval; LS, least squares; mBMI, modified body mass index; mITT, modified intention-to-treat; mNIS+7, modified neuropathy impairment score +7; QoL-DN, quality of life-diabetic neuropathy; R-ODS, Rasch-built Overall Disability Score; SD, standard deviation; SE, standard error mean.

^a Lower scores indicate less impairment/fewer symptoms.

^b Higher values indicate less disability/less impairment, or better nutritional status. mBMI = albumin (g/L) x weight (kg) / height (m²).

Note: Statistically significant results in bold.

In the post hoc analyses comparing the HELIOS-A vutrisiran and patisiran arms, there were no statistically significant differences between vutrisiran and placebo in change from baseline to Month 18, in the primary and all secondary outcomes.

6.29 In the post hoc analyses comparing the HELIOS-A vutrisiran and patisiran arms, there were no statistically significant differences between vutrisiran and patisiran in change from baseline to Month 18, in the primary and all secondary outcomes. The study report also reported that 48.3% of patients (57/118) in the vutrisiran arm and 39.0% of patients (16/41) in the patisiran arm reported improvement in mNIS+7 over 18 months. The evaluation noted that given the differences between vutrisiran and patisiran baseline values in terms of mNIS+7 (total score) and Norfolk QoL-DN, and that the comparison was not powered to detect differences between treatment arms, the lack of statistically significant differences between treatments is not sufficient to establish noninferiority. The Pre-PBAC Response argued that although non-inferiority margins for these outcomes were not defined, the totality of the evidence supports a conclusion that vutrisiran is at least of non-inferior comparative effectiveness to patisiran.

Supportive network meta-analysis

6.30 The submission presented a supportive indirect treatment comparison using a Bayesian network meta-analysis (NMA) of adult patients with hATTR amyloidosis with polyneuropathy with Stage 1 or 2 disease, to assess the comparative efficacy of vutrisiran versus patisiran. The analysis was based on 2 arms from the HELIOS-A study (vutrisiran and patisiran) and 2 arms from the APOLLO study (patisiran and placebo).

6.31 The results of the NMA showed that both vutrisiran and patisiran were superior to placebo in the treatment of adult patients with hATTR amyloidosis with polyneuropathy stage 1 and stage 2, and showed no statistically significant differences between vutrisiran and patisiran in terms of improvement or no change in PND score, change in mNIS+7 and Norfolk QOL-DN score from baseline to Month 18. The evaluation noted there were insufficient data to support noninferiority of vutrisiran

and patisiran within the NMA, given it relied on only two trials, with wide credible intervals and a lack of nominated noninferiority margins. The PSCR argued that the NMA was informative, despite differences in baseline characteristics of patients in the HELIOS-A study compared with the APOLLO study, noting the NMA increased the number of patients for patisiran and resulted in narrower 95% CIs.

Comparative harms

6.32 Key adverse events occurring in the APOLLO study are summarised in Table 8. All safety analyses were performed with the safety population (patients who received at least one dose of the study drug).

Table 8: Summary of patients experiencing adverse events in the HELIOS-A and APOLLO studies

Adverse events, n (%)	HELIOS-A		APOLLO	
	Vutrisiran (n=122)	Patisiran (n=42)	Patisiran (n=148)	Placebo (n=77)
Any adverse events	119 (98%)	41 (98%)	143 (97%)	75 (97%)
Serious AEs, n (%), number of events	32 (26.2%), 63	18 (42.9%), 42	54 (36.5%), 101	31 (40.3%), 99
At least 1 severe adverse event	19 (15.6%)	16 (38.1%)	42 (28.4%)	28 (36.4%)
Treatment discontinuation due to AEs	3 (2.5%)	3 (7.1%)	7 (4.7%)	11 (14.3%)
Study withdrawal due to AEs	3 (2.5%)	2 (4.8%)	7 (4.7%)	9 (11.7%)
Deaths due to AEs	2 (1.6%)	3 (7.1%)	7 (4.7%)	6 (7.8%)
Adverse events related to study drug, n (%)	29 (23.8%)	15 (35.7%)	73 (49.3%)	30 (39.0%)
Infusion related reaction	0	10 (23.8%)	28 (18.9%)	7 (9.1%)

Source: Tables 2.22 to 2.25, pp57-61 of the submission.

Abbreviations: AE, adverse event.

6.33 The proportions of patients reporting any adverse events were high in the HELIOS-A and APOLLO studies, but similar between treatments. In the HELIOS-A study larger proportions of patients treated with patisiran reported one or more severe adverse event (vutrisiran 15.6%; patisiran 38.1%) or serious adverse events (vutrisiran 26.2%; patisiran 42.9%). The proportions of patisiran-treated patients reporting severe adverse events or serious adverse events were higher in the HELIOS-A study compared with the APOLLO study (severe: 38.1% vs 28.4% respectively; serious: 42.9% vs 36.5%, respectively). This is consistent with patients in the HELIOS-A study reporting less severely impacted function in terms of FAP and PND scores at baseline, compared to the APOLLO study.

6.34 In the HELIOS-A study, the most commonly reported adverse events in patients treated with vutrisiran were falls (18.0%), pain in an extremity (14.8%) diarrhoea (13.9%), peripheral oedema (13.1%), urinary tract infection (13.1%), arthralgia (10.7%), and dizziness (10.7%). The most commonly reported adverse events in patients treated with patisiran were infusion related adverse events (23.8%), urinary tract infection (19.0%), diarrhoea (16.7%), falls (14.3%), peripheral oedema (13.1%), headache (11.9%), and constipation (11.9%). No patients in the patisiran arm of HELIOS-A discontinued treatment or study participation due to infusion related adverse events.

- 6.35 The most commonly reported adverse events in the APOLLO study were diarrhoea (patisiran 37.2%; placebo 37.7%), peripheral oedema (29.7%; 22.1%), falls (16.9%; 28.6%), nausea (14.9%; 20.8%), urinary tract infection (12.8%; 18.2%), constipation (14.9%; 16.9%), dizziness (12.8%; 14.3%), muscular weakness (3.4%; 14.3%), and infusion related adverse events (patisiran 18.9%; placebo 9.1%).
- 6.36 Larger proportions of patients in the APOLLO study, treated with patisiran or placebo, reported adverse events compared to the HELIOS-A study. The proportions of patients treated with patisiran reporting infusion related adverse events was similar between studies (HELIOS-A 23.8%; APOLLO 18.9%).

Benefits/harms

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

Clinical claim

- 6.38 The submission described vutrisiran as comparable in terms of effectiveness compared to patisiran and comparable or superior in terms of safety compared to patisiran. The submission noted that vutrisiran provides a decreased burden for patients, caregivers, and the Australian healthcare system by virtue of its once 3 monthly subcutaneous administration, compared to the patisiran once 3 weekly intravenous infusion.
- 6.39 The evaluation considered the therapeutic conclusion presented in the submission was uncertain for the following reasons:
- The claim of noninferior efficacy was supported by a pre-specified noninferiority comparison of vutrisiran versus patisiran in HELIOS-A based on the biomarker, serum TTR. However, supportive evidence from the underpowered post hoc analyses from HELIOS-A relied on a lack of statistically significant differences between vutrisiran and patisiran, there were baseline differences between treatments for some outcomes, wide confidence intervals, and a lack of nominated noninferiority margins. Similarly, the supportive Bayesian NMA, based on only 2 trials, relied on a lack of statistically significant differences between vutrisiran and patisiran, there were wide credible intervals and a lack of nominated noninferiority margins.
 - The long-term comparative efficacy and safety of vutrisiran and patisiran is uncertain, with comparative evidence between vutrisiran and patisiran from the HELIOS-A study limited to 18 months. Limited results are available from the 18-month HELIOS-A extension study (9-month results reported in an abstract/poster; all patients receiving vutrisiran treatment). The PBAC previously considered that the duration of benefit of patisiran (based on the 18-month placebo-controlled APOLLO study) was uncertain due to the limited follow-up (paragraph 7.6 patisiran PSD, July 2023 PBAC meeting).

- It is uncertain whether the results of the HELIOS-A and APOLLO studies are applicable to the Australian setting, given larger proportions of patients in the estimated Australian population (based on AAN registry data) with PND 1 (53.7%), compared to the HELIOS-A (36.0%) and APOLLO (24.9%) studies, and smaller proportions of patients with less progressed disease, particularly PND IIIA, in the Australian setting (7.4%), compared to the HELIOS-A (14.0%) and APOLLO (28.0%) studies. In addition, a history of type 1 diabetes, type 2 diabetes (≥5 years), acute coronary syndrome, uncontrolled cardiac arrhythmias or unstable angina, and there was no evidence presented supporting the use of vutrisiran in these populations. The PSCR noted HELIOS-A enrolled 12 Australian patients, representing a substantial proportion of the 62 patients in Australia with PND scores of 1 or higher (based on AAN registry data) and argued that, despite differences in the distribution of patients across PND scores between HELIOS-A, APOLLO and the Australian population, the efficacy of vutrisiran is consistent across all patients and there is no indication this is limited to a PND subgroup.
- 6.40 The ESC considered the issues raised by the evaluation remained sources of uncertainty with regards to the clinical claims of non-inferior comparative effectiveness and safety of vutrisiran and patisiran. However, the ESC also considered the totality of the evidence, including the comparison based on the surrogate marker of serum TTR, and the available evidence for more patient-relevant outcomes, was supportive of a conclusion that vutrisiran is likely to be comparable to patisiran in terms of comparative effectiveness and safety. Furthermore, the ESC considered that, whilst the approach to compare vutrisiran to placebo was atypical, the available data is supportive of a conclusion that vutrisiran is effective and superior to placebo over a period of at least 18 months (the limit of presented data). The ESC also acknowledged vutrisiran has less burdensome administration requirements than patisiran, which will be preferred by some patients.
- 6.41 The PBAC considered that the claim that vutrisiran is of comparable effectiveness and safety to patisiran was reasonable, noting that uncertainties remained regarding the long-term benefits and risks of both medicines.

Economic analysis

- 6.42 The submission presented a cost-minimisation of vutrisiran versus patisiran for the treatment of adult patients with hATTR amyloidosis and stage 1 or 2 polyneuropathy, over 18 months (HELIOS-A treatment duration). The submission used a modelled approach, with 3 x 6-monthly cycles (with half-cycle correction), incorporating time-dependent risks of treatment discontinuation and mortality. The ESC agreed with the evaluation that the use of a modelled cost-minimisation approach was not adequately justified, and introduced unnecessary complexity to the cost minimisation.
- 6.43 The key components of the cost-minimisation approach are summarised in Table 9.

Table 9: Key components of the cost-minimisation approach

Component	Claim or assumption
Therapeutic claim: effectiveness	Based on evidence presented, the effectiveness of vutrisiran is claimed to be comparable to patisiran.
Therapeutic claim: safety	Based on evidence presented, the safety of vutrisiran is claimed to be to be comparable or superior to patisiran.
Evidence base	A prespecified noninferiority analysis of vutrisiran versus patisiran for the secondary outcome of change in serum TTR in the HELIOS-A study. A post hoc comparison of the vutrisiran and reference patisiran arms of the HELIOS-A study. A supportive network meta-analysis based on the HELIOS-A and APOLLO studies.
Equi-effective doses	Vutrisiran 50.0 mg (2 doses over 6 months, 25.0 mg per dose once every 3 months by subcutaneous injection), is equivalent to Patisiran 223.7 mg (8.696 doses over 6 months, 25.732 mg per dose once every 3 weeks by intravenous infusion).
Direct medicine costs	Vutrisiran effective AEMP: \$ [REDACTED] per 25 mg prefilled syringe. Patisiran effective AEMP: \$ [REDACTED] per 10 mg vial.
Other costs or cost offsets	Premedication costs (patisiran), drug administration costs (vutrisiran and patisiran), costs associated with treating serious infusion related adverse events (patisiran), costs associated with end-of-life care.

Source: Table 3.1, p69 of the submission.

- 6.44 The submission estimated the equi-effective doses of vutrisiran and patisiran over 6 months of treatment, based on recommended dosing regimens: vutrisiran 25 mg (prefilled syringe) once every 3 months by subcutaneous injection; patisiran 0.3 mg/kg bodyweight (to a maximum of 30 mg) by intravenous infusion once every 3 weeks.
- 6.45 Patients treated with vutrisiran were estimated to receive 50 mg every 6 months (i.e. vutrisiran 25 mg once every 3 months × 2). While this is consistent with the proposed product information for vutrisiran, in the HELIOS-A study, vutrisiran dosing every 3 months was defined as every 12 weeks ± 3 days.
- 6.46 Patients treated with patisiran were expected to receive 8.696 administrations every 6 months (52.18 weeks per year × 0.5 years ÷ dose frequency of 3 weeks). The average dose per administration of patisiran was 25.732 mg, based on the distribution of patient weights in the HELIOS-A study (2.5732 vials per patient dose × 10 mg per vial).
- 6.47 The estimated equi-effective doses of vutrisiran versus patisiran were:
- Vutrisiran 50 mg (2 doses over 6 months, 25 mg per dose), is equivalent to
Patisiran 223.77 mg (8.696 doses over 6 months, 25.732 mg per dose).
- 6.48 The equi-effective doses were not adjusted for compliance and assumed perfect adherence and persistence. However, treatment adherence and persistence were incorporated in the estimated costs included in the cost minimisation.
- 6.49 Treatment discontinuations for vutrisiran and patisiran were based on observed risks of treatment discontinuation at Months 9 and 18 in HELIOS-A, converted to monthly rates. The monthly rate derived from treatment discontinuation at Month 9 was used to estimate the proportion of patients on treatment in the first 6 months; and the monthly rate from treatment discontinuation at Month 18 was used to estimate the

proportions of patients on treatment at 12 and 18 months, with appropriate conversion to probabilities.

- 6.50 Mortality for vutrisiran and patisiran was assumed to be the same for both agents (given HELIOS-A was not powered to detect differences in mortality between treatment arms), and was based on vutrisiran mortality data observed in the HELIOS-A study 18 month treatment phase, applied using the same approach used to estimate treatment discontinuations.
- 6.51 Table 10 summarises the costs included in the cost minimisation model.

Table 10: Costs included in the cost minimisation model

Cost	Cost per 6 month cycle		Source
	Vutrisiran	Patisiran	
Drug costs			
Drug acquisition costs	\$■	\$■	Vutrisiran proposed effective AEMP of \$■ per 25 mg prefilled syringe. Drug cost of \$■ per 6 month cycle, assuming recommended dosing regimen (Q3M), adjusted for relative dose intensity of 99.88% (ratio of cumulative number of doses of vutrisiran received by patients in HELIOS-A divided by the total number of doses per protocol). It was assumed that there would be no costs associated with any switching from patisiran to vutrisiran treatment.
			Patisiran effective AEMP of \$■ per 10 mg vial. Calculated assuming recommended dosing regimen (0.3 mg/kg Q3W with a maximum dose of 30 mg), applied to HELIOS-A individual patient weight data to derive weighted average of 2.5732 × 10 mg vials per administration and 8.696 administrations every 6 months, adjusted for relative dose intensity of 96.29% (same method as vutrisiran for HELIOS-A patisiran arm).
Premedication ^a	NA	\$24.68 (\$2.95 per dose)	Drug costs assumed use of selected oral PBS items dexamethasone, paracetamol, H1 antagonist and H2 antagonist, updated to 1 May 2024 Schedule, assuming patisiran administered 8.696 times each 6 month cycle, adjusted for patisiran dose intensity of 96.39%.
Drug administration	\$168.50 (\$84.35 per dose)	-	Administration of vutrisiran by subcutaneous injection in a hospital, based on MBS item 116: Professional attendance at consulting rooms or hospital, by a consultant physician in the practice of the consultant physician's specialty (June 2024 MBS Schedule). MBS fee at time of evaluation \$87.30.
	-	\$995.67 (\$118.90 per dose)	Administration of patisiran by intravenous infusion in a hospital, based on MBS item 13950: Parenteral administration of one or more antineoplastic agents (June 2024 MBS Schedule) ^{a,b} . MBS fee at time of evaluation \$123.05.
Event costs			
Serious treatment-related adverse events	NA	\$148.41	Based on the incidence of treatment-related serious adverse events occurring in ≥2% of patients in either arm of HELIOS-A (vutrisiran: no AEs; patisiran: infusion phlebitis [2.4%], infusion related reactions [7.1%] and infusion site cellulitis [4.8%]); converted to a 6-monthly risk. AR-DRG costs for infusion phlebitis (F63B, \$2,003.34), infusion related reactions (Q61A, Q61B, Q61C; weighted by separations \$2,727.36), infusion site cellulitis (T16B, \$4,080.48).
End-of-life costs ^a	\$134.81 (\$24,602.09 per event)	\$134.81 (\$24,602.09 per event)	Applied to the proportion of patients that die in the model. Based on Reeve et al. (2017), a retrospective study of costs associated with treating Australian patients in their final six months of life, including hospitalisations, emergency department visits, prescription drugs, clinician visits, pathology, and procedures (\$19,696.00), indexed to 2024 dollars using the CPI. ^c

Source: Table 3.7, p74 of the submission.

Abbreviations: AEMP, approved ex-manufacturer price; AR-DRG, Australian Refined Diagnosis Related Group; CPI, consumer price index; MBS, Medicare Benefits Schedule; NA, not applicable; Q3M, once 3 monthly; Q3W, once 3 weekly.

^a Sources and methods as previously considered by the PBAC for patisiran (paragraph 6.48, Patisiran PSD, July 2023 PBAC meeting).

^b DUSC previously considered that MBS item 13950 was not reasonable, given that patisiran is not an antineoplastic agent (Table 15, patisiran PSD, July 2023 PBAC meeting). However, patisiran administration costs had a minimal impact on the cost minimisation.

^c Use of the CPI to inflate costs was inconsistent with the PBAC Guidelines which recommend the AIHW total health price index.

6.52 Costs were included based on the incidence of treatment-related serious adverse events occurring in ≥2% of patients in either arm of HELIOS-A (vutrisiran: no AEs;

patisiran: infusion phlebitis [2.4%], infusion related reactions [7.1%] and infusion site cellulitis [4.8%]); converted to a 6-monthly risk.

- 6.53 End-of-life costs were included in the model, based on Reeve et al. (2017), a retrospective study of costs associated with treating Australian patients in their final six months of life, including hospitalisations, emergency department visits, prescription drugs, clinician visits, pathology, and procedures, indexed to 2024 dollars using the CPI. The inclusion of mortality/end-of-life care costs in the cost minimisation was not adequately justified, given the assumption of no difference between treatment arms.
- 6.54 The costs used in the cost minimisation model are uncertain for the following reasons:
- Costs associated with patisiran were dependent on estimates of treatment persistence, patient weight distribution and the incidence of serious adverse events derived from the small patisiran reference arm in the HELIOS-A study (N=42); which may not provide robust estimates.
 - In HELIOS-A, larger proportions of patients treated with patisiran (42.9%) experienced delayed or missed doses due to COVID-19, compared to vutrisiran (13.9%).
 - The use of selected oral PBS medicines in the estimated costs of premedication was not adequately justified. Costs may be higher than estimated if recommended intravenous formulations of corticosteroids, and H1/H2 blockers are used.
- 6.55 Table 11 presents the results of the cost minimisation of vutrisiran versus patisiran.

Table 11: Results of the cost-minimisation approach over 18 months

Component	Vutrisiran	Patisiran	Incremental costs
Drug costs	\$	\$	\$
Administration costs	\$495	\$2,930	-\$2,435
Premedication costs	\$0	\$73	-\$73
Infusion related adverse events	\$0	\$437	-\$437
End-of-life care related costs	\$336	\$336	0
Total	\$	\$	-\$

Source: Table 3.10, p77 of the submission.

- 6.56 Based on the proposed effective vutrisiran AEMP of \$ [REDACTED] per 25 mg prefilled syringe, the submission estimated that vutrisiran has similar costs to patisiran over 18 months.
- 6.57 The validity of the cost-minimisation approach is dependent on acceptance of the non-inferiority claim for vutrisiran versus patisiran.
- 6.58 Table 12 summarises the results of key sensitivity analyses conducted during the evaluation exploring the impact of alternative vutrisiran and patisiran dosing, and perfect treatment adherence.

Table 12: Key sensitivity analyses

Scenario	Total cost over 18 months			Cost-minimised vutrisiran AEMP
	Vutrisiran (\$)	Patisiran (\$)	Incremental cost	
Base case ^a	\$	\$	-\$	\$
Vutrisiran dosing every 12 weeks (2.17 administrations per 6-month period)	\$	\$	\$	\$ (-8%)
2 vials of patisiran per administration	\$	\$	\$	\$ (-22%)
2.38 vials of patisiran per administration based on APOLLO study (basis of December 2023 PBAC recommendation) ^b	\$	\$	\$	\$ (-7%)
3 vials of patisiran per administration	\$	\$	-\$	\$ (+16%)
Assume perfect adherence	\$	\$	-\$	\$ (+4%)
Treatment-related serious adverse event costs excluded ^c	\$	\$	\$	\$ (0%)
ESC 1: Simplified base case ^d . Modelled aspects removed. Treatment persistence based on based on mean duration of treatment from HELIOS-A.	\$	\$	\$	\$ (-4%)
ESC 2: As per submission base case and ^e : - Vutrisiran dosing every 12 weeks (2.17 administrations per 6-month period); and - 2.38 vials of patisiran per administration based on APOLLO.	\$	\$	\$	\$ (-15%)
ESC 3 (preferred): Combine ESC 1 and ESC 2	\$	\$	\$	\$ (-18%)
Additional analyses considered by the PBAC				
Submission base case and: - Vutrisiran dosing every 87 days; and - 2.38 vials of patisiran per administration based on APOLLO.	\$	\$	\$	\$ (-12%)
Simplified base case ^d and: - Vutrisiran dosing every 87 days; and - 2.38 vials of patisiran per administration based on APOLLO.	\$	\$	\$	\$ (-15%)

Source: Constructed during the evaluation, using the Section 3 Excel cost minimisation workbook

Abbreviations: AEMP, approved ex-manufacturer cost

^a The base case economic evaluation was calculated based on the proposed effective AEMP for vutrisiran (\$ per 25 mg syringe) and effective AEMP for patisiran (\$ per 10 mg vial). Vutrisiran dosing was assumed to be 3-monthly (2 doses per 6-month period). Patisiran dosing was assumed to be 3-weekly (2.57 vials per dose; 8.70 administrations every 6 months).

^b The average number of patisiran vials was calculated to be 2.38 per administration, based on the reported weight distribution for the non-V30M population in the APOLLO study (34-66 kg: 62.0%; 67-99 kg: 34.1%; 100-132 kg: 3.9%), 62% of patients would require 2 vials, and 38% of patients would require 3 vials. The December 2023 resubmission stated that the weight distribution was reflective of the Australian symptomatic patient population based on advice from the Sydney site of the Australian Amyloidosis Network (AAN) (paragraph 18.2 patisiran PSD, December 2023 PBAC meeting).

^c Based on serious treatment-related adverse events occurring in ≥2% of patients in either arm of the HELIOS-A trial.

^d Simplified CMA: Modelling aspects removed (no 6-month cycles or half-cycle correction); treatment persistence revised from modelled time-on-treatment and mortality estimates to mean duration of treatment from HELIOS-A (18.82 months for vutrisiran; 18.08 months for patisiran from Table 14.1.9.1.1 HELIOS-A 18M CSR2 10 JANUARY 2020); adverse event costs for infusion related reactions based on overall incidence of treatment-related serious adverse events occurring in ≥2% of patients in either arm of HELIOS-A (Infusion-site phlebitis 2.38%, Infusion-related reactions 7.14%, Infusion site cellulitis 4.76%); end-of-life costs removed (assumed equal in the modelled analysis).

^e Change INPUTSIE11 to (365.25/2)/(7×12) and INPUTSIJ21 to 2.38.

6.59 The ESC noted that virtually the entire cost in the CMA was due to drug acquisition costs and that the results of the sensitivity analyses indicated that the cost-

minimisation approach is sensitive to the number of vials per administration of patisiran, the frequency of vutrisiran administration, and estimates of treatment persistence. The ESC noted that comparisons between vutrisiran and patisiran safety outcomes were not adequately powered, and included only small numbers of events, and may not be reliable.

- 6.60 The PSCR stated that the HELIOS-A protocol allowed dosing every 12 weeks plus or minus 3 days during the Treatment Period and ± 7 days during the Treatment Extension Period, and argued that a CMA assuming administration of vutrisiran at 12 weekly intervals would overestimate the dose which will be used in practice. However, the ESC noted that the analysis based on vutrisiran dosing every 12 weeks was consistent with the trial evidence which informed the assessment of the clinical claims.
- 6.61 The PSCR reported that the average number of vials used in the patisiran early access program (EAP) in Australia was 2.61. The average utilisation of patisiran was reported to be 2.73 and 2.63 vials per patient, in the US and UK respectively. The ESC noted that the submission assumed an average utilisation of 2.57 vials of patisiran per administration, which was higher than the estimate of 2.38 vials based on the APOLLO study considered by the PBAC in December 2023 (Table 12).
- 6.62 The ESC noted that inputs for the submission's base case CMA were derived from small patient numbers in HELIOS-A, particularly for the patisiran group (vutrisiran n=122, patisiran n=42), and considered these were not robust. The ESC also noted there were several uncertainties with regards to the clinical claims of non-inferior comparative effectiveness and safety of vutrisiran and patisiran, as discussed in paragraph 6.40. The ESC considered that the submission's modelling method was overly complex and not justified, given the limited data to inform the model's time-dependent risks of treatment discontinuation (and mortality). The ESC considered that a simplified model would be a more appropriate basis for the CMA (ESC 1). In addition, the ESC considered that the analysis should assume vutrisiran dosing every 12 weeks (consistent with the HELIOS-A study) and 2.38 vials of patisiran per administration (based on APOLLO study and as considered previously by the PBAC) were appropriate. This ESC preferred multivariate sensitivity analysis (ESC 3 in Table 12) resulted in a cost-minimised vutrisiran AEMP that was reduced by 18% compared with the price proposed in the submission.
- 6.63 The Pre-PBAC Response argued that vutrisiran should not be considered a 'me too' version of patisiran, and it represents a scientific advance in the delivery of small interfering RNA therapies. With respect to the equi-effective doses and dosing intervals, the Response argued that a 3-monthly dosing interval for vutrisiran has been supported by regulatory agencies, and serum TTR data presented (Figure 1) shows the efficacy of vutrisiran is maintained and stable around the 12-week interval period (when vutrisiran was administered according to the HELIOS-A protocol). With respect to the number of vials per patisiran administration, the Response maintained that 2.57 vials is reasonable and based on that used in the HELIOS-A study, and lower than that observed in the Australian EAP, the US or the UK (paragraph 6.61 refers).

Drug cost/patient/year

6.64 Table 13 presents a comparison of drug costs for vutrisiran and patisiran included in the cost-minimisation and financial estimates.

Table 13: Drug cost per patient per year for vutrisiran and patisiran

	HELIOS-A	Cost-minimisation	Financial estimates
Vutrisiran			
Dose regimen	25 mg every 3 months	25 mg every 3 months	25 mg every 3 months
Drug cost per injection	-	\$ (AEMP)	DPMQ \$
Units per administration	-	1	1
Administrations per year	-	4 (3 monthly doses)	4 (3 monthly doses)
Relative dose intensity	NR	99.88% ^a	99.88% ^a
Cost per year	-	\$ (AEMP)	\$ (DPMQ)
Persistence	Discontinued treatment 5 (4.1%)	Months 0-6: 99.2% ^b Months 6-12: 97.8% Months 12-18: 96.6%	Year 1: 97.8% ^b Year 2: 95.3% Year 3: 92.7% Year 4: 90.2% Year 5: 87.7% Year 6: 85.3%
Patisiran			
Dose regimen	0.3 mg/kg every 3 weeks	0.3 mg/kg every 3 weeks	0.3 mg/kg every 3 weeks
Drug cost per vial	-	\$ (AEMP)	DMPQ \$ for 3 vials
Units per administration	-	2.57 ^c	2.57 ^c
Administrations per year	-	17.4 (52.18 weeks per year/3 weekly doses)	17.3 (52 weeks per year/3-weekly doses)
Relative dose intensity	NR	96.29% ^a	96.29% ^a
Cost per year	-	\$ (AEMP)	\$ (DPMQ)
Persistence	Discontinued treatment 4 (9.5%)	Months 0-6: 99.5% ^b Months 6-12: 98.1% Months 12-18: 96.7%	Year 1: 98.1% ^b Year 2: 95.4% Year 3: 92.8% Year 4: 90.3% Year 5: 87.9% Year 6: 85.6%

Source: Constructed during the evaluation based on Section 10.1, p57 of the HELIOS-A Clinical Study Report ('Alylam Pharmaceuticals_HELIOS-A 18M CSR Body_.pdf'), Section 3 Excel cost minimisation workbook, and Section 4 financial implications Excel workbook.

Abbreviations: AEMP, approved ex-manufacturer price; DPMQ, dispensed price for maximum quantity; NR, not reported.

^a Relative dose intensity calculated as ratio of cumulative number of doses of vutrisiran/patisiran received by patients in HELIOS-A divided by the total number of doses per protocol.

^b Based on treatment discontinuation and mortality data from the HELIOS-A study used to determine the proportion of patient on treatment in the cost-minimisation approach.

^c Based on the weight distribution of patients in the HELIOS-A study. This compares with 2.38 units per administration used in the patisiran submission (paragraph 6.81, Patisiran PSD, July 2023 PBAC meeting).

Estimated PBS usage & financial implications

6.65 This submission was not considered by DUSC.

6.66 The submission used an epidemiological approach to estimate the utilisation and financial impacts associated with listing vutrisiran for the treatment of patients with hATTR amyloidosis with polyneuropathy.

6.67 Table 14 presents the key data sources and parameter values applied in the utilisation and financial estimates.

Table 14: Key inputs for financial estimates

Parameter	Value applied and source	Comment
Prevalence of hATTR amyloidosis with polyneuropathy	7.52 per million (0.000752%), based on the estimated non-endemic national prevalence (high value) from Schmidt 2018.	Unchanged from the July 2023 consideration of patisiran. Estimates from Schmidt 2018 were based on a 2014 survey of clinician and epidemiologist members of the European Network for ATTR-FAP (Parman et al. 2016) and may not be applicable to the contemporary Australian setting.
Proportion of eligible patients (PND I-IIIb)	30.77%, based on the estimated distribution of untreated hATTR amyloidosis patients in the Australian Amyloidosis Network (AAN) analysis.	Unchanged from the July 2023 consideration of patisiran. Estimates from the AAN may not represent the broader hATTR population in Australia. The estimate was based on untreated patients only. It is unclear whether excluded treated patients were treated with therapies other than vutrisiran and patisiran.
Incidence of hATTR amyloidosis with polyneuropathy	0.24 per million (0.000024%), based on advice from the AAN, assuming 16 newly diagnosed patients with PND 0 over 5 years, from which 3.2 patients will progress to PND I each year; and 10 newly diagnosed patients with hATTR amyloidosis per year, from which 3.3 patients will progress to PND I each year; divided by the Australian population in the year the data were provided by the AAN (2023: 27,147,199).	Estimates were considered highly uncertain.
Grandfathered patients	█ ¹ vutrisiran patients and █ ¹ patisiran patients, as provided by the sponsor.	Grandfathered patients were inappropriately included in addition to estimates of prevalent patients. In addition, the submission's approach to estimating substituted grandfathered patients appeared to be in error. Substituted grandfathered patients were not adjusted for uptake of vutrisiran and the submission assumed there would be no continuation of treatment beyond year 1; inconsistent with the approach used to estimate utilisation by grandfathered patients for vutrisiran.
Uptake of patisiran in prevalent patients	Yr 1: █%; Yr 2: █%; Yr 3: █1%; Yr 4: █%; Yr 5: █%; Yr 6: █%. Assumption, broadly based on DUSC-proposed uptake rates in PBAC consideration of patisiran (█% in Year 1, increasing to █% in Year 6).	Assumed uptake rates are uncertain.
Uptake of vutrisiran in prevalent patisiran patients	█% in Years 1-6, assumed.	Assumed uptake rates are uncertain.
Uptake of patisiran in incident patients	█% in Years 1-6, assumed.	Assumed uptake rates are uncertain.
Uptake of vutrisiran in incident patisiran patients	█% in Years 1-6, assumed.	Assumed uptake rates are uncertain.

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Parameter	Value applied and source	Comment
Treatment persistence	<p><u>Vutrisiran</u>: Yr 1: 97.8%, Yr 2: 95.3%, Yr 3: 92.7%; Yr 4: 90.2%; Yr 5: 87.7%; Yr 6: 85.3%</p> <p><u>Patisiran</u>: Yr 1: 98.1%; Yr 2: 95.4%; Yr 3: 92.8%; Yr 4: 90.3%; Yr 5: 87.9%; Yr 6: 85.6%</p> <p>Based on persistence estimates in the submission, using treatment discontinuation and mortality data from the HELIOS-A study. Estimates are an average of 6 and 12 monthly persistence each year.</p>	Treatment persistence is likely to be lower in clinical practice compared to the HELIOS-A study.
Treatment adherence	<p><u>Vutrisiran</u>: 99.88%</p> <p><u>Patisiran</u>: 96.29%</p> <p>Relative dose intensity calculated as the ratio of cumulative number of doses of vutrisiran/patisiran received by patients in HELIOS-A divided by the total number of doses per protocol.</p>	This is consistent with the relative dose intensity applied in the cost minimisation.

Source: Section 4, pp150-160 of the submission; Section 4 financial implications Excel workbook.

Abbreviations: AAN, Australian Amyloidosis Network; hATTR, hereditary transthyretin-mediated amyloidosis; PND, polyneuropathy disability; Yr, Year.

The redacted values correspond to the following ranges:

1 < 500

6.68 The estimated utilisation and financial implications of listing vutrisiran (based on effective prices) are presented in Table 15, including revised estimates proposed by the PSCR.

Table 15: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients treated	1	1	1	1	1	1
Number of scripts dispensed ^a	1	1	1	1	1	1
Estimated financial implications of vutrisiran						
Cost to PBS/RPBS less copayments	2	3	3	3	3	3
Estimated financial implications for patisiran						
Cost to PBS/RPBS less copayments	4	4	4	4	4	4
Cost to PBS/RPBS less copayments (PSCR)	4	4	4	4	4	4
Net financial implications to the PBS/RPBS/MBS						
Net cost to PBS/RPBS	2	2	2	2	2	2
Net cost to PBS/RPBS (PSCR)	2	2	2	2	2	2
Net cost to MBS ^b	4	4	4	4	4	4
Net cost to PBS/RPBS/MBS (submission^c)	2	2	2	2	2	2

Source: Table 4.11, p85 of the submission; Section 4 financial implications Excel workbook; Table 3 of the PSCR.

Abbreviations: PBS, Pharmaceutical Benefits Scheme; RPBS, Repatriation Pharmaceutical Benefits Scheme.

^a Based on 4 scripts per patient per year, adjusted by treatment adherence of 99.88%, as estimated in the submission.

^b MBS costs associated with treatment administration: vutrisiran \$98.44 (MBS item 116; 80% Schedule fee); patisiran \$67.48 (MBS item 13950; 80% Schedule fee)

^c MBS costs could not be updated for PSCR-adjusted figures and would change with differential patisiran use, therefore a final net cost to PBS/RPBS/MBS is not presented for PSCR-updated figures.

The redacted values correspond to the following ranges:

1 < 500

2 \$0 to < \$10 million

3 \$10 million to < \$20 million

4 net cost saving

- 6.69 The submission's estimates inappropriately included additional costs for grandfathered patients, who should be accounted for in prevalent population estimates. The ESC agreed with the evaluation that inclusion of additional costs for grandfathered patients was not appropriate, as they should be accounted for in prevalent population estimates.
- 6.70 The PSCR agreed with the evaluation's finding that the submission had made an error when estimating the patisiran utilisation for substituted grandfathered patients. The calculation of substituted grandfathered patients had not been adjusted for uptake of vutrisiran and assumed that there would be no continuation of patisiran treatment beyond year 1; inconsistent with the approach used to estimate utilisation by grandfathered patients for vutrisiran. The PSCR provided updated revised financial estimates to correct for this. These updates were not evaluated, however appear only to impact the cost of substituted patisiran. The utilisation and financial estimates table has been updated to present these alongside the original submission estimates.
- 6.71 The PSCR further argued the suggestion that grandfathered patients should be included in the prevalent population was reasonable if all these patients are receiving treatment with patisiran; however, the assumed uptake of patisiran in 2025 is only 50% of the total eligible population (per Table 14), therefore there are an estimated < 500 patients who are assumed to not commence patisiran treatment in 2025. The Response clarified that there are < 500 patients currently receiving treatment with vutrisiran and these patients are proposed for grandfathering and were assumed to be captured in this non-patisiran population. The PSCR and Pre-PBAC Response stated that none of these patients were expected to substitute patisiran for vutrisiran, and maintained the approach taken by the submission was reasonable. The ESC considered the vutrisiran grandfathered patients should have been included in the prevalent hATTR amyloid population estimates and that the additional estimates (incremental cost of listing) should only include patients that would not have access to, or would be unable to receive, PBS-funded patisiran and, based on the available information, no such patients had been identified.
- 6.72 The estimated net cost to the PBS/RPBS was \$0 to < \$10 million in Year 1, increasing to \$0 to < \$10 million in Year 6, a total cost of \$10 million to < \$20 million over the first 6 years of listing. The net cost despite the cost-minimisation approach, was primarily due to the inappropriate addition of costs associated with grandfathered patients. The estimated net cost to the PBS/RPBS excluding grandfathered patients was \$0 to < \$10 million in Year 1, increasing to \$0 to < \$10 million in Year 6. The submission modelled a difference in adherence assumptions between vutrisiran and patisiran in the financial estimates, however ESC considered differential adherence assumptions may not be reasonable given the severity of hATTR amyloidosis and given most patients are closely monitored and managed in practice.

Financial Management – Risk Sharing Arrangements

- 6.73 The submission did not propose a risk sharing arrangement. The PBAC recommended listing patisiran at the December 2023 PBAC meeting, after outstanding issues of concern had been resolved by a commitment from the sponsor for reassessment of the cost effectiveness of patisiran in 3 years, further amendments to revised financial estimates, and a revised risk sharing arrangement (paragraph 19.1, 19.5, Patisiran PSD, December 2023 PBAC meeting). The PBAC advised that the review of cost-effectiveness 3 years after PBS listing should be included in a Deed of Agreement, and noted that the review may affect the future PBS price of patisiran (paragraph 19.7, 19.9, patisiran PSD, December 2023 PBAC meeting).
- 6.74 Given the cost-minimisation approach presented for vutrisiran versus patisiran, the abovementioned review would also affect the future price of vutrisiran. The PSCR indicated that the sponsor is willing to include data on vutrisiran in the planned review of patisiran at 3 years post listing. The ESC considered it would be appropriate for PBAC to make this a mandatory requirement, as it was for patisiran, by specifying the relevant details in a Deed of Agreement. The ESC noted there is an OLE phase of the HELIOS-A study which is currently ongoing and will capture clinical data for patients treated with up to 5 years of vutrisiran treatment and that, in any case, the timeline of the PBAC review of patisiran at 3 years post-PBS listing should remain unchanged. The pre-PBAC response stated that the sponsor has no objection to including a requirement for a cost effectiveness review in the Deed of Agreement for vutrisiran.

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

7 PBAC Outcome

- 7.1 The PBAC recommended the Section 100 (Highly Specialised Drugs Program - Public and Private Hospitals), Authority Required listing of vutrisiran for the treatment of hereditary transthyretin mediated (hATTR) amyloidosis in patients with stage 1 or 2 polyneuropathy. In making this recommendation, the PBAC considered that the available evidence supported a claim that vutrisiran is of comparable effectiveness and safety to patisiran, however uncertainties remained regarding the long-term benefits and risks of both medicines. The PBAC recalled that when recommending patisiran for listing in December 2023, it had considered long term cost-effectiveness of patisiran was uncertain due to limitations of the available trial evidence, and advised that a review of cost-effectiveness should be conducted three years after PBS listing of patisiran. The PBAC advised that a reassessment of vutrisiran should be conducted at the same time as the scheduled patisiran review, no later than three years after PBS listing of patisiran. The PBAC considered, given the comparable effectiveness and safety to patisiran, that the listing should not result in any additional net cost to Government.
- 7.2 The Committee advised the equi-effective doses were vutrisiran 25 mg given once every 12 weeks and patisiran at a dose of 0.3 mg/kg body weight (maximum 30 mg)

given once every 3 weeks (assuming an average of 2.38 vials of patisiran per administration), based on the regimens used in the respective clinical trials for these agents.

- 7.3 With respect to the requested listing, the PBAC considered listing in the Section 100 - Highly Specialised Drugs Program was appropriate. Specifically, the PBAC considered vutrisiran to be a highly specialised drug with a high unit cost, and patients were typically engaged with a hospital-based clinic (with treatment likely to be initiated in this context), but it was also reasonable to allow the drug to be administered in a primary care setting if clinically appropriate, noting that the recommended restriction includes treatment criteria specifying that the patient must be treated by a consultant with experience in the management of amyloid disorders or in consultation with a consultant with experience in the management of amyloid disorders. Therefore, the PBAC considered it was appropriate for vutrisiran to be able to be dispensed in both the hospital pharmacy setting and in the community setting (see paragraph 3.4). The Committee considered the other elements of the listing should align with the current listings of patisiran, including being a written authority, and noted the restrictions for both medicines include a criterion that excludes concomitant usage of vutrisiran and patisiran.
- 7.4 The Committee considered there was a clinical need for additional effective therapies for hATTR amyloidosis and associated polyneuropathy, however noted the clinical outcomes achieved with vutrisiran are likely to be similar to patisiran. The PBAC acknowledged the input from individuals and organisations supporting the listing and highlighting the benefits of less frequent and burdensome administration compared to patisiran. Therefore, the PBAC considered there was a clinical place for vutrisiran as an alternative treatment to patisiran and that as a subcutaneous injection given once every 3 months, vutrisiran would be more convenient for some patients than patisiran, which is administered by IV infusion once every 3 weeks.
- 7.5 The PBAC considered the nominated comparator of patisiran was appropriate.
- 7.6 The PBAC noted the submission was supported by one small RCT (HELIOS-A) comparing vutrisiran (n=122) to patisiran (n=42), and data derived from an external placebo arm (n=77) of the pivotal trial for patisiran (APOLLO). The PBAC noted that to accept the results of such a comparison, it must be accepted that HELIOS-A and APOLLO are sufficiently exchangeable for this purpose. The Committee noted there were differences in the populations and disease severity in the vutrisiran arm of HELIOS-A and the placebo arm of APOLLO (paragraph 6.14 refers) and considered the overall approach of using an external placebo reference arm increased inherent uncertainty to such a comparison. These issues notwithstanding, the PBAC considered the HELIOS-A study was a reasonable basis to consider the comparative effectiveness of vutrisiran and patisiran, although there were differences in disease severity and that reliance on a surrogate marker (serum TTR) as the primary basis to support the clinical claim was a source of uncertainty. The PBAC acknowledged, that larger and more robust clinical trials in hATTR amyloidosis would be difficult to undertake due to

the rarity and severity of the condition and considered the available evidence in that context.

- 7.7 With respect to comparative effectiveness, the PBAC noted the results of HELIOS-A found no statistically significant differences between vutrisiran and patisiran for the clinical outcomes including change in mNIS+7 score and other outcomes (see Table 7), but agreed with the evaluation that differences in baseline characteristics between arms resulted in a lack of statistically significant differences being unreliable for assessing a claim of non-inferior comparative effectiveness. The PBAC further noted the results for serum TTR levels from baseline to 18 months met the pre-specified threshold for statistical non-inferiority (see Figure 1 and paragraph 6.27) and considered these results were supportive that vutrisiran achieves a comparable reduction in serum TTR to patisiran over this period. Whilst serum TTR is a surrogate marker and not a direct clinical outcome, based on the limited evidence available the PBAC considered that serum TTR provided the most reliable data for assessing the relative efficacy of vutrisiran and patisiran. For the comparison with the external placebo reference arm from APOLLO, the PBAC noted that the results for all primary and secondary outcomes favoured vutrisiran and the differences were statistically significant. Overall, the PBAC considered the available evidence suggested vutrisiran and patisiran were similar in terms of comparative effectiveness but reiterated that conclusion was based on a surrogate biomarker and longer-term data on clinical outcomes would be informative.
- 7.8 In terms of comparative safety, the PBAC considered the claim of comparable safety of vutrisiran and patisiran was reasonable. The Committee noted the submission presented a summary of adverse events across the HELIOS-A and APOLLO studies, and considered the differences in baseline characteristics made a reliable comparison across these trials difficult. The PBAC noted the safety results from HELIOS-A found similar but low number of adverse events across treatments, and considered the low number precluded a robust comparison of the safety of vutrisiran and patisiran. However, given the overall numerical similarity in adverse event rates between therapies, the PBAC was satisfied that the safety profiles of vutrisiran and patisiran are likely to be comparable.
- 7.9 The PBAC considered the submission's cost minimisation approach (CMA), which used a modelled approach was overly complex and not justified, given the limited data available to inform the model. The PBAC noted the results were almost entirely driven by drug acquisition costs. The PBAC agreed with the ESC that a simpler approach to the CMA was preferred (paragraph 6.59 refers) and that the CMA should be based on equi-effective doses derived from the trials (see paragraph 7.2). The PBAC considered that the analysis preferred by the ESC (ESC 3 in Table 12) was an appropriate cost minimisation approach, noting that this was based on a simplified approach, with the modelled aspects removed (6-month cycles and half-cycle correction). In this approach:

- Treatment persistence was based on based on mean duration of treatment from HELIOS-A (vutrisiran 18.82 months, patisiran 18.08 months), rather than modelled time-on-treatment and mortality estimates.
 - Infusion-related serious adverse event costs were based on overall incidence in HELIOS-A (infusion-site phlebitis 2.38%, infusion-related reactions 7.14%, infusion site cellulitis 4.76%) rather than rate per 6 month period.
 - End of life costs were removed.
 - The PBAC considered that the analysis should assume vutrisiran dosing every 12 weeks (consistent with the HELIOS-A study) and 2.38 vials of patisiran per administration (based on APOLLO study as considered previously by the PBAC). The PBAC noted that APOLLO included more patients receiving patisiran than HELIOS-A and that the disease severity in APOLLO was more applicable to the PBS population and therefore that the comparative dosing of patisiran should be the same as accepted in the patisiran study.
- 7.10 As discussed above (paragraphs 7.2 and 7.9), the PBAC considered it was appropriate to assume vutrisiran dosing every 12 weeks (84 days) in the cost minimisation approach. However, the PBAC also noted that in the HELIOS-A trial, vutrisiran 25 mg SC injection was administered every 12 weeks \pm 3 days during the treatment period and every 12 weeks \pm 7 days during the treatment extension period (paragraph 6.60). On this basis, the PBAC considered that the analysis shown as ESC 3 in Table 12 was appropriate for the cost minimisation, however a small adjustment to the dosing interval for vutrisiran would be acceptable, consistent with the clinical trial protocol for HELIOS-A. The PBAC noted the additional analysis shown in Table 12, that assumed a dosing interval of 87 days and considered that a cost minimisation approach that assumed a dosing interval in the range 81 days to 87 days would be acceptable.
- 7.11 The PBAC considered the utilisation and financial estimates, which were based on the estimates for patisiran, were generally reasonable for estimating the size of the treated population, as the Australian hATTR population is small and well-defined. The Committee considered the uptake rates estimated in the submission were likely reasonable as uptake was expected to be high owing to the less onerous administration requirements compared to patisiran. The PBAC also considered it was appropriate for vutrisiran to join the patisiran Risk Sharing Arrangement (RSA). The Committee agreed with the ESC that the grandfathered population would be captured in the prevalent population estimates and did not accept the argument in the PSCR and Pre-PBAC Response that the expected grandfathered patients currently treated with vutrisiran would never have otherwise commenced treatment with patisiran (paragraph 6.71 refers). The PBAC recalled that it had previously given detailed advice regarding the eligible patient population and financial estimates for patisiran in July 2023, September 2023 and December 2023 (Patisiran PSD, July 2023 PBAC meeting, September 2023, December 2023 addenda). Thus the PBAC did not accept the sponsor's request to add additional grandfathered patients to the financial

estimates for the purposes of the RSA.

- 7.12 The PBAC noted the Deed of Agreement for patisiran includes a clause requiring a review of its cost effectiveness 3 years after PBS listing (which occurred on 1 August 2024), as advised by the PBAC in December 2023 (paragraph 19.9, patisiran PSD, December 2023 PBAC meeting). Given the nature of the clinical data for vutrisiran, which relies on the effectiveness of patisiran over placebo to be affirmed to assess its cost effectiveness, the PBAC considered vutrisiran should be subject to the same cost-effectiveness review requirements. The PBAC advised that the cost-effectiveness review may impact the future PBS price of vutrisiran, noting that a price reduction would be needed if the review found that patisiran and/or vutrisiran were less cost-effective based on updated data informing the review. The PBAC noted that, consistent with its advice for patisiran, there would be no basis for a price increase for vutrisiran (paragraph 15.7 patisiran PSD, December 2023 PBAC meeting).
- 7.13 The PBAC noted that the open-label extension phase of the HELIOS-A study is ongoing and will capture clinical data for patients treated with up to 5 years of vutrisiran treatment. The submission presented an interim analysis of the extension study period at 9 months (poster/abstract only; Obici et al 2023), corresponding to 27 months of vutrisiran treatment, including the initial 18-month treatment period (6.24, 6.25). The PBAC noted the estimated study completion date is October 2026², which would allow the results to be considered at the time of the patisiran review. The PBAC considered that the timeline of the PBAC review of patisiran at 3 years post-PBS listing should remain unchanged. The PBAC considered that evidence from HELIOS-A including the extension phase would provide the basis for the reassessment as discussed above. In addition, the PBAC advised that the sponsor should be required to provide a systematic literature review, to ensure that any relevant clinical evidence for vutrisiran including single arm studies, and comparisons with either patisiran or placebo, is presented for consideration in a manner consistent with the PBAC guidelines. If the literature review identifies any relevant studies beyond the HELIOS-A extension phase, these should also be presented within the submission for PBAC consideration.
- 7.14 The submission should present all relevant clinical evidence as described in 7.13. In addition, consistent with its previous advice for patisiran, the PBAC considered that its future reassessment of vutrisiran should consider: 1) whether the data were supportive of long term benefits of vutrisiran (based on QOL and PND score); 2) whether updated mortality data supported a survival benefit; 3) whether updated safety data were consistent with the safety data in the submission and whether any new clinically significant safety signals were evident; and 4) whether vutrisiran was

² <https://clinicaltrials.gov/study/NCT03759379>, accessed 6 November 2024.

cost-effective in the PBS population, based on the updated evidence base. In addition, for vutrisiran, whether the updated body of evidence, including serum TTR data, remained supportive of the claim of non-inferior relative efficacy and safety of vutrisiran and patisiran in the PBS population. The PBAC noted that the sponsor would be required to submit both a cost-utility analysis for vutrisiran compared with placebo, and a cost minimisation approach for vutrisiran compared with patisiran, to support this review. The PBAC noted that the current submission was based on a cost-minimisation approach versus patisiran, however considered that a cost-utility analysis versus placebo should also be presented by the sponsor to support the review, because this would allow the sponsor to provide a comprehensive analysis of the benefits and costs of vutrisiran based on updated evidence. The PBAC would expect that the same, or very similar model to that presented for patisiran would also be presented for vutrisiran.

- 7.15 The PBAC advised that the requirement for vutrisiran to be considered at the same time as the scheduled review of patisiran at three years post the date of patisiran listing should be documented in a Deed of Agreement with the sponsor, including an expectation that the sponsor will provide a submission to the PBAC to inform a review of the cost-effectiveness of vutrisiran as described in paragraphs 7.12 to 7.14. The Committee noted the sponsor had agreed to the inclusion of vutrisiran in such a review (paragraph 6.74 refers).
- 7.16 The PBAC recommended that vutrisiran should be treated as interchangeable on an individual patient basis with patisiran, according to s101(3BA) advice.
- 7.17 The PBAC advised that vutrisiran is not suitable for prescribing by nurse practitioners.
- 7.18 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 patisiran, or not expected to address a high and urgent unmet clinical need given the presence of an alternative therapy, the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were not met.
- 7.19 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:

Recommended

8 Recommended listing

8.1 Add new items:

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
VUTRISIRAN					
vutrisiran 25 mg/0.5 mL injection, 0.5 mL syringe	NEW	1	1	1	Amvuttra

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Restriction Summary / Treatment of Concept:	
	Category / Program: <input checked="" type="checkbox"/> Section 100 – Highly Specialised Drugs Program – Public (Code HB) / Private (Code HS)
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
	Restriction type: <input checked="" type="checkbox"/> Authority Required (FULL assessment) in writing only via post/HPOS upload)
	Authority type: <input checked="" type="checkbox"/> Complex Authority Required (CAR)
	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: 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.
	Episodicity:
	Severity:
	Condition: Hereditary transthyretin amyloidosis
	Indication: Hereditary transthyretin amyloidosis
	Treatment Phase: Initial treatment
	Clinical criteria:
	Patient must not have previously received PBS-subsidised treatment with this drug for this PBS indication
	AND
	Clinical criteria:
	The condition must be hereditary transthyretin amyloidosis confirmed by genetic testing
	AND
	Clinical criteria:
	Patient must have a Polyneuropathy Disability (PND) score description of either I, II, IIIA, IIIB; OR
	Patient must have a Familial Amyloid Polyneuropathy (FAP) stage description of 1 or 2
	AND
	Clinical criteria:
	Patient must not have previously undergone a liver transplant
	AND
	Clinical criteria:
	Patient must not exhibit heart failure symptoms (defined as New York Heart Association NYHA class III or IV)
	AND
	Treatment criteria:
	Must be treated by a consultant with experience in the management of amyloid disorders or in consultation with a consultant with experience in the management of amyloid disorders
	AND
	Treatment criteria:
	Patient must be undergoing treatment with this drug as a monotherapy (i.e. not in combination with any other disease modifying medicines for amyloidosis disorders)

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	AND
	Population criteria:
	Patient must have either: (i) stage 1 polyneuropathy, (ii) stage 2 polyneuropathy
	AND
	Population criteria:
	Patient must be at least 18 years of age
	Prescribing Instructions: PND scores in the context of this PBS restriction are:, Stage 0 - No symptoms; Stage I - Sensory disturbances but preserved walking capability; Stage II - Impaired walking capacity but able to walk without stick or crutches; Stage IIIA - Walking with help of one stick or crutch; Stage IIIB - Walking with help of two sticks or crutches; Stage IV - Confined to wheelchair or bedridden.
	Prescribing Instructions: FAP stage in the context of this PBS restriction are:, Stage 0 - No symptoms; Stage 1 - Unimpaired ambulation; Stage 2 - Assistance with ambulation required; Stage 3 - Wheelchair-bound or bedridden.
	Prescribing Instructions: Applications for authorisation under this treatment phase must be made via the Online PBS Authorities System (real time assessment) or in writing via HPOS form upload or mail. If the application is submitted through HPOS form upload or mail, it 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).

Restriction Summary / Treatment of Concept:	
	Category / Program:
	<input checked="" type="checkbox"/> Section 100 – Highly Specialised Drugs Program – Public (Code HB) / Private (Code HS)
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
	Restriction type: <input checked="" type="checkbox"/> Authority Required (FULL assessment) in writing only via post/HPOS upload)
	Authority type: <input checked="" type="checkbox"/> Complex Authority Required (CAR)
	Indication: Hereditary transthyretin amyloidosis
	Treatment Phase: Continuing treatment
	Clinical criteria:
	Patient must have previously received PBS-subsidised treatment with this drug for this condition
	AND
	Clinical criteria:
	Patient must continue to demonstrate clinical benefit
	AND
	Clinical criteria:
	Patient must have had a Polyneuropathy Disability (PND) score description of either I, II, IIIA, IIIB prior to commencing non-PBS subsidised therapy; OR Patient must have had a Familial Amyloid Polyneuropathy (FAP) stage description of 1 or 2 prior to commencing non-PBS subsidised therapy.
	AND
	Clinical criteria:
	Patient must not have previously undergone a liver transplant
	AND
	Clinical criteria:
	Patient must not have exhibited heart failure symptoms (defined as New York Heart Association [NYHA] class III or IV) prior to commencing non-PBS subsidised therapy.
	AND
	Clinical criteria:

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	Patient must not be permanently bedridden; OR Patient must not be receiving end-of-life care
	AND
	Treatment criteria:
	Must be treated by a consultant with experience in the management of amyloid disorders or in consultation with a consultant with experience in the management of amyloid disorders
	Treatment criteria:
	Patient must be undergoing treatment with this drug as a monotherapy (i.e. not in combination with any other disease modifying medicines for amyloidosis disorders)
	Prescribing Instructions: Applications for authorisation under this treatment phase must be made via the Online PBS Authorities System (real time assessment) or in writing via HPOS form upload or mail., If the application is submitted through HPOS form upload or mail, it 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).

Restriction Summary / Treatment of Concept:	
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	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
	Restriction type: <input checked="" type="checkbox"/> Authority Required (FULL assessment) in writing only via post/HPOS upload)
	Authority type: <input checked="" type="checkbox"/> Complex Authority Required (CAR)
	Indication: Hereditary transthyretin amyloidosis
	Treatment Phase: Transitioning from non-PBS to PBS-subsidised supply - Grandfather arrangements
	Clinical criteria:
	Patient must have received treatment with this drug for this condition prior to [PBS listing date]
	AND
	Clinical criteria:
	Patient must continue to demonstrate clinical benefit
	AND
	Clinical criteria:
	Patient must not be permanently bedridden; OR Patient must not be receiving end-of-life care
	AND
	Treatment criteria:
	Must be treated by a consultant with experience in the management of amyloid disorders or in consultation with a consultant with experience in the management of amyloid disorders
	Treatment criteria:
	Patient must be undergoing treatment with this drug as a monotherapy (i.e. not in combination with any other disease modifying medicines for amyloidosis disorders)
	Prescribing Instructions: Applications for authorisation under this treatment phase must be made via the Online PBS Authorities System (real time assessment) or in writing via HPOS form upload or mail., If the application is submitted through HPOS form upload or mail, it 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).

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.