Technology Guidance

Eplontersen and vutrisiran

for hereditary transthyretin amyloidosis with polyneuropathy

Technology Guidance from the MOH Drug Advisory Committee

Guidance Recommendations

The Ministry of Health's Drug Advisory Committee has recommended:

- ✓ Vutrisiran 25 mg/0.5 mL injection for stage 1 or 2 hereditary transthyretin amyloidosis with polyneuropathy (hATTR-PN).

Funding status

Vutrisiran 25 mg/0.5 mL injection is recommended for inclusion on the Medication Assistance Fund (MAF) for the abovementioned indication from 1 September 2026.

Patient must be undergoing treatment with vutrisiran as a monotherapy (i.e. not in combination with any other disease modifying medicines for amyloidosis disorders), and treatment should be used in line with the additional clinical criteria listed in the Annex.

MAF assistance **does not** apply to any formulations or strengths of eplontersen for treating hATTR-PN.

Updated: 1 July 2026

Technology evaluation

1.1. At the November 2025 meeting, the MOH Drug Advisory Committee ("the Committee") considered the evidence presented for the technology evaluation of both eplontersen and vutrisiran for treating stage 1 or 2 hereditary transthyretin amyloidosis with polyneuropathy (hATTR-PN). The Agency for Care Effectiveness (ACE) conducted the evaluation in consultation with clinical experts from public healthcare institutions and patient experts from local patient and voluntary organisations. Clinical and economic evidence for eplontersen and vutrisiran was considered in line with their registered indication.

1.2. The evidence was used to inform the Committee's deliberations around four core decision-making criteria:

- Clinical need of patients and nature of the condition;
- Clinical effectiveness and safety of the technology;
- Cost effectiveness (value for money) – the incremental benefit and cost of the technology compared to existing alternatives; and
- Estimated annual technology cost and the number of patients likely to benefit from the technology.

1.3. Additional factors, including social and value judgments, may also inform the Committee's funding considerations.

Clinical need

2.1. hATTR is an adult-onset, autosomal-dominant disease caused by mutations in the transthyretin (*TTR)* gene, and primarily presents as polyneuropathy (PN) and/or cardiomyopathy (CM). Patients with hATTR-PN experience progressive nerve damage, increased disability, and reduced ability to work and carry out daily activities.

2.2. The Committee heard that all 34 known hATTR-PN patients in public healthcare institutions have a mixed PN and CM phenotype. The predominant local variant (A97S) progresses rapidly, with worsening cardiac involvement leading to heart failure and increased mortality. Eplontersen and vutrisiran are TTR gene-silencing therapies that reduce TTR protein production and amyloid deposition by degrading TTR mRNA in hepatocytes. Eplontersen is an antisense oligonucleotide, while vutrisiran is a small-interfering RNA. Both drugs are HSA-approved for treating hATTR-PN.

2.3. The Committee noted the currently limited treatment options for hATTR-PN and the high unmet need for affordable treatments. Diflunisal is used off-label but has limited supporting evidence and is associated with adverse effects that restrict its long-term use. Tafamidis is HSA-approved and listed on the Medication Assistance Fund (MAF) for wild-type or hereditary ATTR-CM only. While some patients with mixed PN/CM phenotype may receive tafamidis, its effectiveness for hATTR-PN remains uncertain. Patisiran, another TTR gene-silencing therapy, is not locally registered and is currently accessed only by a small proportion of patients with adequate private insurance coverage; it was therefore excluded from this evaluation. As a result, symptomatic management alone was used as the comparator for both eplontersen and vutrisiran, with an additional comparison conducted between the two treatments.

2.4. The Committee considered four testimonials from local patients about their lived experiences with hATTR and the treatments they have received. The Committee acknowledged that the condition had a significant negative impact on patients' mobility, quality of life and ability to care for themselves because of symptoms such as numbness in all four limbs and losing fine motor control, which made it challenging to perform activities such as retrieving items from pockets and moving around unaided.

2.5. The Committee heard that three respondents with mixed PN/CM phenotype receiving patisiran or tafamidis felt the treatments did not improve their symptoms but helped to slow disease progression and had manageable side effects. The Committee noted that two respondents were familiar with eplontersen and vutrisiran through online sources and their peers in patient support groups. These respondents heard that these drugs can be self-administered at monthly or three-monthly intervals without hospitalisation and can effectively improve their symptoms. Most respondents were willing to consider new treatments if they effectively reduced disease progression, improved symptoms and were affordable.

Clinical effectiveness and safety

Eplontersen versus symptomatic management alone and vutrisiran versus symptomatic management alone

3.1. The Committee reviewed evidence from two pivotal phase III, open-label trials for eplontersen (NEURO-TTRansform) and vutrisiran (HELIOS-A), as add-on to symptomatic management in adults with genetically confirmed stage 1 or 2 hATTR-PN. Both trials relied on indirect comparisons with historical placebo groups from earlier hATTR-PN trials (NEURO-TTR and APOLLO respectively). The Committee considered these comparisons to be at a high risk of bias due to baseline differences across arms, imbalances in discontinuation rates, and the open-label study design, which may potentially overestimate treatment benefits.

3.2. The primary and key secondary outcomes of both trials included changes from baseline in the modified Neuropathy Impairment Score+7 (mNIS+7), Norfolk Quality of Life Questionnaire–Diabetic Neuropathy (Norfolk QoL-DN), and serum TTR concentration.

3.3. The Committee heard that in NEURO-TTRansform, eplontersen showed a statistically significant delay in progression and disability compared with the external placebo arm across all three co-primary endpoints (mNIS+7, Norfolk QoL-DN, and serum TTR concentration) at the interim analysis at week 35. A trend towards increasing benefit was observed at the final analysis at week 65/66, although no formal statistical testing was performed. The mNIS+7 results at week 66 met the minimal clinically important difference (MCID) and was considered clinically significant.

3.4. The Committee heard that in HELIOS-A, vutrisiran showed a statistically significant delay in disease progression and disability versus external placebo in both mNIS+7 (primary outcome) and Norfolk QoL-DN (secondary outcome) at month 9, with an increasing magnitude of benefit at month 18. Clinically significant differences were observed for Norfolk QoL-DN (at months 9 and 18) and mNIS+7 (month 18).

3.5. Overall, the Committee considered that it is likely that eplontersen and vutrisiran as an add-on to symptomatic management are superior in efficacy compared with symptomatic management alone for treating hATTR-PN. However, the long-term effectiveness of these treatments remains uncertain.

3.6. In terms of safety, both eplontersen and vutrisiran were generally well-tolerated, with most adverse events (AEs) being mild or moderate and consistent with hATTR-PN. However, given uncertainties in whether the AEs were attributable to the disease or treatment, and reliance on external placebo comparisons, the Committee considered it reasonable to conclude that both treatments had an inferior safety profile compared with symptomatic management alone, given that they are active therapies.

Eplontersen versus vutrisiran

3.7. In the absence of direct evidence comparing eplontersen and vutrisiran, the Committee reviewed indirect treatment comparisons, which included unanchored matching-adjusted indirect comparisons and simulated treatment comparisons of eplontersen (from NEURO-TTRansform) and vutrisiran (from HELIOS-A).

3.8. Results suggested that eplontersen and vutrisiran are likely to have similar efficacy, as between-arm differences in relevant endpoints showed wide 95% confidence intervals crossing zero. However, the Committee agreed that these findings should be interpreted with caution due to the absence of a pre-specified non-inferiority margin, the need to extrapolate eplontersen outcomes to align with HELIOS-A timepoints, differences in mNIS+7 scoring and TTR assays used in the trials, and potential residual confounding in the unanchored comparisons.

3.9. In terms of safety, eplontersen and vutrisiran are likely to have similar safety profiles based on a naïve comparison of AE frequencies, although uncertainties remain given the indirect nature of the comparison, heterogeneity in patient populations, and differing AE reporting timepoints.

Cost effectiveness

4.1. The Committee reviewed an adapted cost-utility analysis comparing vutrisiran versus symptomatic management alone for treating adults with genetically confirmed stage 1 or 2 hATTR-PN based on results from HELIOS-A and APOLLO. At the proposed price, the model showed a base-case incremental cost-effectiveness ratio (ICER) more than SG$365,000 per quality-adjusted life year. The Committee considered the ICER to be high and uncertain due to several model limitations, including the absence of cardiac involvement in the health states despite its relevance to the local hATTR-PN population, and the assumption of constant treatment effects despite uncertain long-term effectiveness. The ICER was also sensitive to transition probabilities, overall survival assumptions, utility values, and the time horizon.

4.2. Given that clinical evidence suggested that eplontersen and vutrisiran are likely to have similar efficacy and safety profiles, the Committee agreed that a cost-minimisation approach was appropriate to assess their cost effectiveness. Overall, based on the companies' proposals, the Committee considered the treatment costs for both eplontersen and vutrisiran to remain high and unaffordable, and did not represent cost-effective use of healthcare resources.

Estimated annual technology cost

5.1. The Committee noted that the cost impact to the public healthcare system for either drug was estimated to be less than SG$1 million in the first year and between SG$1 million and SG$3 million in the fifth year of listing on the MOH List of Subsidised Drugs for treating stage 1 or 2 hATTR-PN.

Recommendations (November 2025)

6.1. Based on available evidence, the Committee recommended not listing eplontersen or vutrisiran on the MOH List of Subsidised Drugs for treating stage 1 or 2 hATTR-PN. This decision was based on unfavourable cost effectiveness at the prices proposed by the companies.

Updated recommendations (April 2026)

7.1. At the April 2026 meeting, the Committee noted that the revised proposal for vutrisiran was adequate to improve its cost effectiveness and manage the uncertainty of the overall budget impact. Hence, the Committee recommended that vutrisiran 25 mg/0.5 mL injection be listed on the Medication Assistance Fund (MAF) for treating stage 1 or 2 hATTR-PN.

7.2. The Committee recommended not listing eplontersen on the MOH List of Subsidised Drugs for hATTR-PN due to unfavourable cost effectiveness compared with vutrisiran.

ANNEX

MAF clinical criteria for vutrisiran for treating hereditary transthyretin amyloidosis with polyneuropathy (hATTR-PN)

Treatment of stage 1 or 2 hereditary transthyretin amyloidosis with polyneuropathy (hATTR-PN):

Additional clinical criteria (initial):
The patient on initial application for stage 1 or 2 hATTR-PN:

- has a confirmed genetic diagnosis of hATTR; and
- has Polyneuropathy Disability (PND) score description of I, II, IIIA, or IIIB or a Familial Amyloid Polyneuropathy (FAP) stage description of 1 or 2; and
- must not have previously undergone a liver transplant; and
- must not exhibit heart failure symptoms (defined as New York Heart Association [NYHA] class IV).

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).

Patient must be treated by, or in consultation with, a specialist physician experienced in the diagnosis and management of hATTR-PN.

An initial assessment of clinical benefit should be conducted 9 months after treatment initiation. Assessment of clinical benefit should combine physical examination and evaluation of autonomic symptoms, alongside validated assessment tools for hATTR-PN (e.g. PND score, Rasch-built Overall Disability Scale [R-ODS], 10-Meter Walk Test [10-MWT], or other objective measures of mobility).

The above criteria are valid for 9 months. To continue treatment, please reapply under 'Renewal'.

Additional clinical criteria (renewal):
The patient on subsequent reapplication for stage 1 or 2 hATTR-PN:

- must not be permanently bedridden or receiving end-of-life care.

Reassessments should be conducted at least every 6 months, and treatment continued only if there is clear evidence of ongoing clinical benefit.

VERSION HISTORY

Guidance on eplontersen and vutrisiran
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This Version History is provided to track any updates or changes to the guidance following the first publication date. It is not part of the guidance.

1. **Publication of guidance**

Date of Publication	1 Feb 2026

2. **Guidance updated to reflect listing of vutrisiran on the Medication Assistance Fund (MAF)**

Date of Publication	1 Jul 2026

Agency for Care Effectiveness - ACE Agency for Care Effectiveness (ACE)

About the Agency

The Agency for Care Effectiveness (ACE) was established by the Ministry of Health (Singapore) to drive better decision-making in healthcare through health technology assessment (HTA), clinical guidance, and education.

As the national HTA agency, ACE conducts evaluations to inform government funding decisions for treatments, diagnostic tests and vaccines, and produces guidance for public hospitals and institutions in Singapore.

The guidance is not, and should not be regarded as, a substitute for professional or medical advice. Please seek the advice of a qualified healthcare professional about any medical condition. The responsibility for making decisions appropriate to the circumstances of the individual patient remains with the healthcare professional.

Find out more about ACE at https://www.ace-hta.gov.sg/about-us/

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