Canada's Drug and Health Technology Agency

CADTH Reimbursement Review

CADTH Reimbursement Recommendation

(Draft)

eplontersen (Wainua)

Indication: For the treatment of polyneuropathy associated with stage 1 or stage 2 hereditary transthyretin amyloidosis (hATTR) in adults.

Sponsor: AstraZeneca Canada Inc.

Recommendation: Reimburse with Conditions

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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Recommendation

The Canadian Drug Expert Committee (CDEC) recommends that eplontersen be reimbursed for the treatment of polyneuropathy (PN) associated with stage 1 or stage 2 hereditary transthyretin amyloidosis (hATTR) in adults only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

One phase III, randomized, open-label trial (NEURO-TTRansform) in adults with hATTR-PN demonstrated that, compared with an external placebo group (NEURO-TTR), treatment with eplontersen resulted in an improvement in neurological function as measured by the modified Neuropathy Impairment Score +7 (mNIS+7) (least squares mean difference [LSMD] at week 66, -24.76 points [95% CI, -30.96 to -18.56]) and health-related quality of life (HRQoL) as measured by the Norfolk Quality of Life–Diabetic Neuropathy Questionnaire (Norfolk QoL-DN) (LSMD at week 66, -19.74 points [-25.63 to -13.84]), which were outcomes important to patients. Additionally, treatment with eplontersen resulted in reduced circulating TTR levels compared to placebo (LSMD at week 65, -70.42% [95% CI, -75.17 to -65.66]).

There is a lack of direct comparative evidence for eplontersen compared to other treatments for hATTR-PN. As such, comparative evidence available for this review was based on the sponsor's matching adjusted indirect treatment comparisons (MAIC), which evaluated the comparative efficacy of eplontersen versus inotersen, patisiran, and vutrisiran. Overall, the MAICs were subject to important limitations and there was generally insufficient evidence to suggest that eplontersen was better or worse than other established treatment options for hATTR-PN, with most estimates affected by serious imprecision. Thus, CDEC could not draw conclusions on the comparative efficacy of eplontersen.

Patients identified a need for treatments that improve patient and caregiver convenience and patient independence, that require less frequent dosing, as well as a treatment that halts disease progression and improves HRQoL. Additionally, patients and clinicians highlighted the need for a treatment that has a lower risk of AEs, including falls. CDEC noted that eplontersen met some of the needs identified by patients by providing another subcutaneous drug option that can be administered in a patient's home, however, it was unknown whether the potential at-home administration method with a pre-filled pen is less burdensome for patients and improves HRQoL relative to administration by a healthcare provider for other treatments, as this was not explicitly studied. CDEC also highlighted that compared to placebo, HRQoL and neurological function remained stable, though the impact of eplontersen relative to other comparators remains unknown. Eplontersen also had a similar safety profile to other TTR silencers with no new safety concerns observed, however, uncertainty remained given the relatively small sample sizes.

At the sponsor submitted price for eplontersen and publicly listed price for all comparators, eplontersen was more costly or similar in cost compared to currently available treatments for hATTR-PN. As there is insufficient evidence to suggest that eplontersen is more effective than its comparators, the total drug cost of eplontersen should not exceed the total drug cost of the lowest-cost funded treatment for hATTR-PN.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation, Renewal, Discontinuation, and Prescribing		
1. Eligibility for eplontersen should be based on the criteria used by each of the public drug plans for initiation, renewal, and prescribing of vutrisiran for hATTR-PN.	There is no evidence that eplontersen is clinically superior or inferior to relevant comparators currently reimbursed for hATTR-PN. The clinical expert noted that the place in therapy for eplontersen is comparable to that of the other TTR silencers (i.e. vutrisiran, patisiran and inotersen).	Genetic testing is required to confirm a diagnosis of hATTR to differentiate this condition from other causes of amyloidosis.
Pricing		
2. Eplontersen should be negotiated so that it does not exceed the drug program cost of treatment with the least costly treatment reimbursed for hATTR-PN.	There is insufficient evidence to justify a cost premium for eplontersen over the least costly treatment reimbursed for hATTR-PN.	—

hATTR-PN = hereditary transthyretin-mediated amyloidosis; TTR = transthyretin.

Discussion Points

- There was uncertainty with the clinical evidence, therefore CDEC considered the criteria for significant unmet need described in section 9.3.1 of the Procedures for CADTH Reimbursement Reviews. CDEC acknowledged the rarity and severity of this condition, which allowed for greater uncertainty of the evidence; however, CDEC considered the submitted evidence to be insufficient to justify a price premium for eplontersen relative to other available treatments.
- CDEC discussed the eligibility criteria of the NEURO-TTRansform study, which excluded patients who have previously used, or were using other TTR-lowering therapies (this included tafamidis, inotersen, patisiran, and off-label use of diflunisal). CDEC noted that in the NEURO-TTRansform study, nearly 70% of patients had exposure to tafamidis or diflunisal, however, CDEC highlighted that there is no evidence to support switching from other therapies in hATTR-PN to eplontersen.
- The NEURO-TTRansform study demonstrated that eplontersen results in a statistically significant reduction in circulating TTR, and an improvement in neurological function, and HRQoL compared to placebo. However, CDEC emphasized most of the evidence informing this review was rated as having low certainty as determined by the GRADE approach (moderate certainty for serum TTR levels), generally related to the study design, and lack of minimally clinical important difference thresholds, which reduced the certainty of evidence for eplontersen relative to placebo. CDEC also discussed that serum TTR reduction may demonstrate biological plausibility but has not been identified as a validated surrogate for clinical efficacy in patients with hATTR-PN. CDEC also discussed the applicability of other outcomes of the NEURO-TTRansform study; including the mNIS+7 and Norfolk QoL-DN, where CDEC heard from the clinical experts consulted for this review, are not used in routine clinical practice, but are demonstrative of efficacy. CDEC also discussed the results for outcomes relevant to clinical practice per the clinical experts (COMPASS-31 and R-ODS), which were exploratory and non-comparative in the NEURO-TTRansform study, and although mostly uninterpretable, were generally supportive of the effect of eplontersen.
- CDEC discussed the administration method and schedule of eplontersen and relevant comparators as eplontersen is administered by subcutaneous injection once monthly, vutrisiran is administered subcutaneously every 3 months, patisiran is administered by IV every 3 weeks, and inotersen is administered subcutaneously once weekly. The clinical experts consulted for this review highlighted that the choice between therapies is guided by availability, route and frequency of administration, patient preference, and contraindications. CDEC concluded that there was no evidence that assesses the impact of the administration and dosing of eplontersen on efficacy outcomes.
- CDEC discussed the safety profile observed with eplontersen. Due to the open-label, external cohort design of the NEURO-TTRansform study and relatively small sample size, the interpretation of safety events attributable to eplontersen is challenging as all patients received the same treatment. CDEC also discussed the lack of long-term safety and tolerability data. However, CDEC agreed with the clinical experts consulted for this review that overall, the incidence and severity of

adverse events (AEs), particularly ocular AEs related to Vitamin A deficiency, were considered tolerable, manageable, and similar to other drugs in this setting.

- CDEC discussed the uncertainty of the comparative efficacy of eplontersen due to the absence of direct comparative evidence. CDEC considered the sponsor-submitted matching adjusted indirect comparison (MAIC) that compared eplontersen to vutrisiran, patisiran, and inotersen. However, numerous limitations (including small sample sizes, and heterogeneity across study designs and populations) in the analyses, and wide 95% CIs that included the potential for no difference or that either treatment could be favoured meant that there was generally insufficient evidence for CDEC to draw conclusions on the efficacy of eplontersen versus relevant comparators in hATTR-PN.
- CDEC discussed the uncertainty in the number of patients who would be eligible for treatment with eplontersen. If the prevalence of hATTR-PN be higher than estimated, the budget impact of reimbursing eplontersen will be greater.

Background

Transthyretin (TTR) amyloidosis is a rare, systemic, and life-threatening disease resulting from the deposition of amyloid in multiple tissues. TTR amyloidosis is characterized by the abnormal deposition of TTR protein in various organs, leading to organ dysfunction. Hereditary transthyretin amyloidosis (hATTR) is a genetic condition caused by an autosomal dominant mutation in the TTR gene, which leads to the production of unstable TTR proteins, which are primarily produced in the liver, that are more prone to misfolding and amyloid deposition. Accumulation of misfolded amyloid fragments in a range of organ systems causes a variety of motor, sensory, and autonomic neuropathies leading to progressive muscle weakness and disability, pain, wasting, gastrointestinal dysfunction, and other autonomic symptoms such as orthostatic hypotension. The peripheral nervous system and the cardiac system are heavily affected, leading to two of the primary manifestations of the disease – polyneuropathy (PN) and cardiomyopathy (CM), respectively.

Clinically, hATTR often progresses rapidly and leads to worsening sensorimotor neuropathy, a condition that damages the patient's sensory and motor nerves, escalating a patients' disability over time. Beyond sensorimotor neuropathy, the disease can also instigate a progressive autonomic neuropathy, which affects the nerves controlling the body's automatic functions, including digestion, leading to gastrointestinal impairment, weight loss, and cachexia. In the clinical setting, polyneuropathy associated with hereditary transthyretin amyloidosis (hATTR-PN) is assessed and classified using two key staging systems: the polyneuropathy disability (PND) score and familial amyloid polyneuropathy (FAP) staging system (developed by Coutinho). hATTR-PN can be characterized as early (i.e., in patients less than 50 years) or late (i.e., in patients 50 years or older) onset, though there is significant worldwide variability regarding age of onset. The life expectancy of patients with hATTR-PN ranges from 10 to 15 years following the time of symptoms developing.[4] The median survival from the time of diagnosis in hATTR-PN is 4.7 years.

hATTR-PN is an ultra-rare disease affecting approximately 10,000 individuals worldwide, though the condition may be underdiagnosed. The clinical experts consulted for this review also noted that misdiagnosis is common as neuropathy can be attributed to many other diseases. The highest prevalence of hATTR-PN has been observed in northern Portugal and northern Sweden (as high as 50 per 100,000 inhabitants). There is a lack of published Canadian prevalence estimates.

Diagnosis of hATTR-PN should include gene sequencing to identify TTR variants and amyloid detection with tissue biopsy or bone scintigraphy scans. According to the 2019 consensus recommendation, the minimum criteria to establish the diagnosis of symptomatic hATTR include: "at least one quantified or objective symptom or sign definitively related to the onset of symptomatic hATTR; or at least one probably related symptom plus one abnormal definitive or confirmed test result; or two abnormal definitive or confirmed test results in the absence of clinical symptoms". The list of tests and investigations for the follow up of TTR mutation carriers includes clinical evaluation, neurophysiology assessment, biomarkers measurement, and cardiac evaluation.

There have been two primary treatments authorized for market use in Canada for managing hATTR-PN: patisiran and inotersen. The 2022 Canadian Guidelines recommend the use of both patisiran and inotersen as first-line treatments for managing hATTR-PN. Recently, vutrisiran also received a recommendation for reimbursement with conditions by CADTH for the treatment of stage 1 or stage 2 PN in adult patients with hATTR.

Eplontersen has been approved by Health Canada for the treatment of PN associated with stage 1 or stage 2 hATTR in adults. Eplontersen is a GalNAc conjugated antisense oligonucleotide (ASO) that selectively binds eplontersen to the TTR messenger RNA

(mRNA) in hepatocytes causing the degradation of TTR mRNA and preventing the synthesis of TTR protein in the liver, resulting in significant reductions in the levels of TTR protein in circulation. It is available as a pre-filled pen for subcutaneous injection and the dosage recommended in the product monograph is 45 mg once monthly.

Sources of Information Used by the Committee

To make its recommendation, the committee considered the following information:

- a review of 1 phase 3 randomized, open label study in patients with hATTR; and 2 indirect treatment comparisons
- patients' perspectives gathered by 1 patient group, Transthyretin Amyloidosis Canada (TAC)
- input from public drug plans that participate in the CADTH review process
- 2 clinical specialists with expertise diagnosing and treating patients with hATTR-PN
- input from 1 clinician group, the Neuromuscular Disease Network for Canada (NMD4C)
- a review of the pharmacoeconomic model and report submitted by the sponsor

Stakeholder Perspectives

Patient Input

One patient group submitted input for this submission: Transthyretin Amyloidosis Canada (TAC); a not-for-profit organization which supports individuals living with all forms of transthyretin amyloidosis, including hATTR and wt-ATTR, through community support, research, and education. Qualitative and quantitative information was gathered from a 23-question online survey of 30 patients, 12 individual interviews, and a round table discussion (sample size not reported). Across sources, input was gathered from a total of 51 patients and caregivers across Canada. All respondents were over the age of 65.

All therapies approved by Health Canada have varying degrees of public reimbursement in different provinces. Additionally, TAC noted that all therapies have undesirable side effects and prohibitive costs and administration schedules. As such, the patient group input highlighted the need for additional treatment options, as well as treatments that have more convenient modes of administration or dosing schedules. Additionally, treatments that improve quality of life (QoL) were important for patients with hATTR.

The patient group input highlighted that currently available treatments have their benefits and side effects. TAC noted that not every therapy has equal efficacy in all patients. As such, allowing patients and physicians access to different treatment options, particularly in a rare, multi-system diseases such as hATTR, is paramount in ensuring no patient is left behind. Among 30 patient and caregiver survey respondents, 83% cited travel for appointments and/or infusions as highly or somewhat invasive, with some of the reported challenges for both the patient and the caregiver including the time required for travel and for the infusion, costs associated with travel and parking, costs of medications, and taking time away from work and other activities. It was also noted that decreased hospital admission is an important outcome of treatment to patients, highlighting that many patients are older and have frail immune systems. As a result, 80% felt that home administration was an important attribute for a new therapy, highlighting that self-administration of therapy will result in greater freedom and less reliance on infusion networks and clinic visits, as well as fewer missed workdays.

The patient group highlighted that loss of autonomy and independence has the greatest impact on QoL according to patients and caregivers. Of the 30 survey respondents, 67% emphasized that hATTR impacted their ability to maintain their career causing them to either stop work, retire early, or scale back to less than 15 hours per week. Additionally, 80% of respondents felt that hATTR had a significant or somewhat significant impact on their ability to travel. In all qualitative interviews, patients expressed that hATTR has a significant impact on their ability to maintain their social life, indicating that their identity is engrossed in their disease, which is partially due to the need to constantly be planning their lives around medical and infusion appointments.

None of the patients had experience with eplontersen. However, all respondents from the qualitative interviews, as well as feedback obtained during the 2-hour roundtable meeting, spoke to the void eplontersen can fill as the only therapy that may be self-administered.

Clinician Input

Input From Clinical Experts Consulted by CADTH

The clinical experts shared that currently, there are no therapies available that can reverse neuropathy in hATTR. The primary aim of existing treatments in hATTR-PN is to decelerate the disease's progression, which ultimately leads to loss of physical functioning and reduced QoL. Currently available disease-modifying therapies have some important limitations and carry risks of significant morbidity and mortality including the potential for severe adverse events (AEs) with inotersen and burdensome infusion schedule with patisiran. With all therapies, there is also a risk of Vitamin A deficiency, requiring supplementation to prevent vision loss. As such, the clinical experts highlighted the need for additional therapies with better efficacy and safety profiles to avoid possible AEs, as well as therapies with formulations that improve convenience, and the potential to switch to more tolerable therapies in patients with hATTR-PN. Despite some treatments administered subcutaneously, offering convenience, current treatments still require healthcare assistance for administration, thus, the clinical experts noted that an ideal treatment would be able to be self-administered by patients or caregivers, either using an auto-injector or orally.

Since the approval of disease-modifying therapy, patients with hATTR-PN in Canada receive one of either inotersen, patisiran, or vutisiran (which has recently received a recommendation to reimburse with conditions from CDEC), which are considered the standard of care in Canada. According to the clinical experts consulted by for this review, eplontersen would be used similarly to other first-line treatment options (iontersen, patisiran, or vutrisiran) and clinical decision between eplontersen and other available disease-modifying therapies would be based on AE profile and convenience. The clinical experts also noted that patients should be able to switch between approved treatments based on tolerance and/or convenience, and that failure of other disease-modifying drugs would not be a prerequisite. The clinical experts noted that there is no evidence to support combining disease-modifying treatments, as combining TTR silencers is unlikely to provide much additional clinical benefit, though the theoretical rationale of combining TTR silencers and TTR-stabilizers could be explored. The clinical experts highlighted that it is likely that existing patients may have tried pharmacotherapies such as inotersen, patisiran, or tafamidis, or undergone treatments such as liver transplantation. They noted that eplontersen may be favoured over the newly available vutrisiran given the less frequent dosing requirements. Overall, the experts highlighted that based on the mechanism of action, eplontersen may offer potential improvements in efficacy, safety, and patient convenience, which could position it favorably against existing treatments.

According to the clinical experts, the patients most suitable for eplontersen treatment are those with confirmed neuropathy and a pathogenic mutation in the TTR gene, confirmed by genetic testing. The clinical experts noted that accessibility of genetic testing in Canada has improved significantly, with initiatives by pharmaceutical companies and provincial labs now offering free testing that includes methods such as saliva or cheek swabs, in addition to traditional blood tests, though awareness of genetic testing is inconsistent across Canada. The experts noted that the ideal patients for treatment with eplontersen are those who mirror the participants in the relevant clinical trials, specifically adults with confirmed neuropathy determined through diagnostic assessments such as nerve conduction studies or evaluations of small fibers to accurately ascertain the presence and extent of neuropathy. Patients with confirmed neuropathy and TTR mutation, and who experience rapid progression of neuropathy are generally most in need of intervention and should be offered treatment as soon as possible. The clinical experts noted that these patients are most likely to experience a noticeable benefit from eplontersen treatment as these patients typically exhibit more pronounced symptoms. Additionally, the clinical experts noted that eplonstersen may prove particularly advantageous for patients who have not adequately responded to other treatments, or for those seeking a therapy with a less burdensome administration schedule, which can significantly impact QoL. Conversely, patients with very advanced neuropathy (e.g., are bedbound) may not have much clinical benefit from a neuropathy perspective and are traditionally excluded from trials.

The overarching goal of hATTR-PN treatment is to stabilize disease progression. Any improvement in symptoms would also be considered a sign of successful treatment. Other critical outcomes of hATTR-PN treatment include improvements in mortality and serious complications requiring hospitalization.

Outcomes of trials in hATTR are generally not feasible for clinical practice and are not used outside trials. Clinically, patients are assessed with neurologic examination. Some centers may use patient reported outcomes to follow patients, but this is not standardized across Canada. Nerve conduction studies and small fiber assessments to evaluate large and small fiber function may be conducted. Other non-standardized assessments include autonomic function tests to gauge patient experiences such as the Composite Autonomic Symptom Score (COMPASS) scale and track neuropathy severity with the Toronto Clinical Neuropathy scale (TCNS), the Overall Neuropathy Limitation Scale (ONLS), and the Rasch Built Overall Disability scale (R-ODS) for neuropathies. Beyond these clinical and diagnostic measures, emphasis is placed on the patient's overall functioning and QoL, which are gauged through comprehensive clinical evaluation, clinical history, and discussions about daily activities.

According to the clinical experts, the primary reason for discontinuation of treatment is severe AEs. Additionally, objective disease progression (e.g. upper and lower extremity functional deterioration) despite treatment at a rate similar to the natural history of hATTR may also be considered a reason for discontinuation.

According to the clinical experts consulted for this review, PN, complex and advanced large and small fiber neuropathies, as well as autonomic neuropathies are diagnosed by a neurologist with training in neuromuscular medicine and experience with similar biologic therapies used in other neuromuscular disorders. Given the rarity of hATTR, neuromuscular neurologists, or neurologists with experience treating hATTR would be required to prescribe and monitor treatment and follow up. The clinical experts highlighted that specialized care would ideally be administered in a hospital or clinic setting equipped with the necessary capabilities and resources to comprehensively manage all facets of advanced neuropathy, including associated cardiac and autonomic symptoms.

Clinician Group Input

One clinician group provided input for this review, the Neuromuscular Disease Network for Canada (NMD4C). The NMD4C is a pan-Canadian network that brings together the country's leading clinical, scientific, technical, and patient expertise to improve care, research, and collaboration in neuromuscular disease. In total 7 clinicians with experience in treating hATTR-PN, and who contributed to published Canadian guidelines for hATTR-PN provided input for this submission.

Treatment goals highlighted by the NMD4C were consistent with those noted by the clinical experts consulted for this review and included the prevention of disease progression, decreased mortality and morbidity, fewer hospital visits, and enhanced QoL. However, the clinician group and the clinical experts consulted for this review emphasized the need for improved efficacy and tolerability, as well as providing options with greater convenience and adherence.

Given that the clinical manifestations of hATTR occur after significant build-up of amyloid has occurred in the body, the NMD4C emphasized that the earlier a therapy is initiated, the better the outcomes are. Patients who present with several different disease manifestations including mainly polyneuropathy and cardiomyopathy are most in need of intervention given the significant morbidity and mortality, and reduced QoL. The NMD4C stated that patients in the early stages of disease (Stage 1 or 2 PN) will demonstrate a better response to treatment. The NMD4C and the clinical experts consulted for this review agreed that it is unknown whether failure to respond to one treatment indicates that failure of a different treatment would occur, thus, having multiple treatment options available is important. Though not the first drug approved, the NMD4C noted that, in their opinion, eplontersen may have advantages over inotersen, not only regarding side effects but also in effectiveness.

In line with the clinical experts consulted for this review, the NMD4C highlighted that outcome measures often used in trials in hATTR are not feasible for clinical practice due to the extensive testing and training required for their use. To determine whether a patient is responding to treatment in clinical practice, the NMD4C and the clinical experts consulted for this review follow the recommendations described in Canadian treatment guidelines and use neurological history, neurological examination, and nerve conduction studies. The NMD4C noted that clinically meaningful responses to treatment would be stability or slower progression of the symptoms and functional abilities, as well as improved survival compared to the natural history of the disease.

Both the NMD4C and the clinical experts consulted for this review agreed that disease progression may be a reason for discontinuation. In clinical practice, outcomes such as loss of walking ability despite intensive treatment could help identify those who are not responding to treatment.

Both the clinician group and the clinical experts consulted for this review stated that neurology and neuromuscular specialists would be required to prescribe and monitor treatment and follow up. The most appropriate settings include specialized and multidisciplinary tertiary centers with lines of referral to cardiologists. The NMD4C also highlighted that hospital outpatient neuromuscular clinics, and community-based neurological clinics and referral lines to neuromuscular expertise may also be appropriate.

Drug Program Input

The clinical experts consulted by CADTH provided advice on the potential implementation issues raised by the drug programs.

Table 2: Responses to Questions from the Drug Programs

Implementation issues	Response
Relevant comparators	
The submitted trial, NEURO-TTRansform, was a phase 3, multicenter, open-label, RCT. There was a treatment arm, and a reference arm (inotersen-eplontersen), with effects compared to an external placebo arm from the NEURO-TTR trial. Given the rare and life-threatening nature of hATTR-PN, and the existence of approved therapies, an active placebo-arm was considered unethical. The sponsor also conducted ITCs to currently available treatment options. Inotersen and patisiran are reimbursed in most, but not all federal, provincial, and territorial jurisdictions. Vutisiran, another relevant comparator, only recently received a CDEC recommendation to reimburse.	Comment from the drug programs to inform CDEC deliberations.
Considerations for initiation of therapy	

If recommended for reimbursement, would it be appropriate to consider aligning with the initiation criteria for vutrisiran:
• Adult patients with genetically confirmed, stage 1 or stage 2 hATTR-PN who are symptomatic with early-stage neuropathy, defined as:
  ○ PND stage I to ≤ IIIB, or FAP stage I or II
  ○ No severe heart failure symptoms (defined as NYHA class III or IV)
  ○ No previous liver transplant
	CDEC agreed with the clinical experts highlighting that there has been little change in the treatment landscape for hATTR-PN, thus, aligning the initiation criteria for eplontersen with the most recently recommended therapy, vutrisiran, is reasonable.

Considerations for continuation or renewal of therapy	
Primary endpoints of the NEURO-TTRansform trial included change from baseline in serum TTR concentration, change from baseline in neuropathy using the mNIS+7 score, and change from baseline in HRQoL using the Norfolk QoL-DN scoring scale. Although the pivotal study used various tools to assess response to treatment, CDEC noted in a previous review for this indication, that monitoring is completed by continuous clinical assessments, with timing depending on disease severity, ranging from every 3 to 6 months or more. With no clearly defined renewal criteria for patisiran, inotersen, or vutisiran, consistency with currently used approaches for monitoring in clinical practice settings would be reasonable.	CDEC and the clinical experts noted that these criteria are in line with clinical practice but highlighted that patients may be seen more frequently initially if there are safety concerns or concerns related to cardiac disease, as this is a contraindication for treatment.

Implementation issues	Response
As such, if recommended for reimbursement, would it be appropriate to consider aligning with the renewal criteria for vutrisiran: An initial clinical assessment of treatment response should occur 9 months after treatment initiation. Thereafter, patients should be assessed at least every 6 months.	
Considerations for discontinuation of therapy	

If recommended for reimbursement, would it be appropriate to consider aligning with the discontinuation criteria for vutrisiran:
• Treatment should be discontinued for patients who are:
  ○ Permanently bedridden and dependent on assistance for basic activities of daily living, or
  ○ Receiving end-of-life care.
	CDEC and the clinical experts were in agreement with the discontinuation criteria for eplontersen being aligned with those of vutrisiran.

Considerations for prescribing of therapy	
Is there any scenario in which a combination of TTR silencers (RNA-targeted treatments [e.g., inotersen, patisiran, or vutrisiran]) or TTR stabilizers (e.g., tafamidis) would be used to treat a patient with hATTR-PN?	For neuropathy, CDEC noted that there is no evidence showing that combining a silencer and stabilizer provides additional clinical benefit. The clinical experts consulted for this review hypothesized that the role of stabilizers in the neurological indication is likely minimal considering the efficacy of silencers in reducing TTR.
If recommended for reimbursement, would it be appropriate to consider aligning with the prescribing criteria for vutrisiran: • The patient must be under the care of a specialist with experience in the diagnosis and management of hATTR-PN. Treatment should not be used in combination with other interfering ribonucleic acid drugs or transthyretin stabilizers used to treat hATTR.	CDEC and the clinical experts agreed with the alignment of prescribing conditions for eplontersen and vutrisiran citing that it may be difficult for a general neurologist to diagnose this rare disease. Most provinces have neuromuscular physicians or community neurologists with expertise in treating neuromuscular disease, thus, since hATTR-PN is a rare disease, most patients would be under the care of these specialists.
Generalizability	
The sponsor noted that eplontersen is expected to displace inotersen. Is there a timeframe or other factor to indicate when this switch may occur? Under what conditions would it be appropriate to switch from inotersen, patisiran, or vutisiran to eplontersen?	The clinical experts noted that patients may choose to switch treatments for various reasons (AEs, dosing schedule, patient preference, etc.), but was noted by both CDEC and the clinical experts that there is currently no evidence supporting switching from inotersen, patisiran, or vutisiran to eplontersen. Regarding the displacement of inotersen, the clinical experts were not aware of any patients that are currently using inotersen. For those who are currently using inotersen, the clinical experts indicated that it would be reasonable to switch them to an alternative treatment option such as eplontersen.
Care provision issues	
Patients in the NEURO-TTRansform trial required genetic testing for diagnostic confirmation and documentation of TTR gene mutations to be eligible for treatment. Is diagnostic confirmation by genetic testing required to initiate treatment in patients with hATTR-PN in Canada? How readily available is genetic testing for hATTR?	The clinical experts highlighted that patients are often misdiagnosed with other types of neuropathies and may not receive genetic testing for hATTR. However, genetic testing for hATTR is readily available through commercial or in-province services, conducted using point-of-care methods.

Implementation issues	Response
System and economic issues	
The sponsor noted that clinicians expect eplontersen to mainly displace inotersen, and perhaps some patisiran patients in the rare occasion a switch is deemed appropriate. Given the rarity of the condition, the sponsor did not expect the total market size to change with the introduction of eplontersen.	As previously noted, the clinical experts stated that in their experience, no patients are currently using inotersen, and they did not expect the market size to shift.
There are confidential negotiated prices for patisiran and inotersen. There was a recent CDEC recommendation for reimbusement of vutrisiran, which has not yet been negotiated by pCPA.	Comment from the drug programs to inform CDEC deliberations.

AE = adverse event; CDEC = Canadian Drug Expert Committee; hATTR = hereditary transthyretin amyloidosis; ITC = indirect treatment comparison; mNIS+7 = modified Neuropathy Impairment Score plus 7; Norfolk QoL-DN = Norfolk Quality of Life Questionnaire-Diabetic Neuropathy; pCPA = pan-Canadian Pharmaceutical Alliance; PN – polyneuropathy; RCT = randomized controlled trial; RNA = ribonucleic acid; TTR = transthyretin.

Clinical Evidence

Systematic Review

Description of Studies

Only 1 study was included in this review. The NEURO-TTRansform study was an 85-week, phase 3, multicentre, randomized, open-label study evaluating the efficacy and safety of eplontersen in patients with hATTR. In total, 168 patients were randomized 6:1 to receive 45 mg eplontersen SC once every 4 weeks (n = 144) or 300 mg inotersen SC once per week for up to 34 weeks and were then switched to eplontersen (hereinafter referred to as inotersen-eplontersen) SC once every 4 weeks from Week 37 to Week 81 (n = 24). The NEURO-TTRansform study was conducted in 40 sites in 15 countries (from North America, Europe, and South America/Australasia/Asia), including 2 sites in Canada (British Columbia and Ontario) that enrolled 3 patients. There were three analysis timepoints in the NEURO-TTRansform study: week 35 (interim analysis), week 65/66 (final analysis), and week 85 (end of treatment analysis). Three co-primary endpoints were used at the final analysis: the percent change from baseline in serum TTR, the change from baseline in modified Neuropathy Impairment Score +7 (mNIS+7), and the change from baseline in Norfolk Quality of Life Questionnaire-Diabetic Neuropathy (QoL-DN).

The NEURO-TTRansform study also included an external control group using the placebo arm (n = 60) from the NEURO-TTR study. NEURO-TTR was a phase II/III double-blind, placebo-controlled study that compared the efficacy and safety of inotersen 300 mg SC injection weekly with placebo in patients with Stage 1 or 2 hATTR-PN. Eligibility criteria for the NEURO-TTR and NEURO-TTRansform studies were identical. Analyses were adjusted for select baseline covariates using propensity scores.

Baseline characteristics of the eplontersen group of NEURO-TTRansform and the external placebo group of the NEURO-TTR study were generally well balanced. In the NEURO-TTRansform study, the mean age was 53.0 years (standard deviation [SD] = 15.0) in the eplontersen group. The mean age in the placebo group of the NEURO-TTR study was 59.5 years (SD = 14.1). In NEURO-TTRansform, most patients had Stage 1 hATTR-PN (115 [79.9%]), as well as Val30Met (V30M) mutations (85 [59.0%]), while in the NEURO-TTR placebo group, 42 (70.0%) patients had Stage 1 hATTR-PN, and 33 (55.0%) had V30M mutations. In NEURO-TTRansform eplontersen group at baseline, the mean serum TTR was 0.2 g/L (SD = 0.1), the mean mNIS+7 composite score was 81.2 (SD = 43.4), and the mean Norfolk QoL-DN total score was 44.1 (SD = 26.6). In the NEURO-TTR placebo group, the mean serum TTR was 0.2 g/L (SD = 0.04). Patients in the NEURO-TTR study may have had less severe disease than patients enrolled in the NEURO-TTRansform study as the mean mNIS+7 composite score was 74.8 (SD= 39.0), and mean Norfolk QoL-DN total score was 48.7 (SD = 26.8).

Efficacy Results

Change from Baseline in mNIS+7 Composite Score

The change from baseline in mNIS+7 composite score was a coprimary endpoint of the NEURO-TTRansform study at the interim and final analyses. At week 35, the LSM change from baseline was 0.22 points (95% CI, -3.46 to 3.90) for eplontersen and 9.23 points (95% CI, 5.54 to 12.91) for external placebo, representing a LSM difference of -9.01 points (95% CI, -13.48 to -4.54), in favour of eplontersen. At week 66, the LSM change from baseline was 0.30 points (95% CI, -4.46 to 5.06) for eplontersen and 25.06 points (95% CI, 20.23 to 29.88) for external placebo, representing a LSM difference of -24.76 points (95% CI, -30.96 to -18.56), in favour of eplontersen. At both timepoints, the reduction in mNIS+7 scores corresponded to an improvement in the severity of neuropathy when treated with eplontersen.

Results for the pre-specified sensitivity analyses were consistent at the interim and final analyses and with the primary analysis, with point estimates for the LSM differences ranging from [redacted] at Week 35 and [redacted] at Week 65 [redacted] across sensitivity analyses.

The treatment effect of eplontersen on mNIS+7 composite score across prespecified subgroups was consistent with the overall population, at the interim and final analyses.

For the exploratory analysis of eplontersen and inotersen-eplontersen groups at Week 35, the mean change from baseline in mNIS+7 composite score was -0.03 points (SD = 16.28) for eplontersen-treated patients (n = 137) and 4.06 points (SD = 13.39) following treatment with inotersen (n = 19).

Change from Baseline in Norfolk QoL-DN Total Score

The change from baseline in Norfolk QoL-DN total score was a key secondary endpoint of the NEURO-TTRansform study at the Week 35 interim analysis and a co-primary endpoint at the Week 66 final analysis. At week 35, the LSM change from baseline was -3.12 points (95% CI, -7.19 to 0.96) for eplontersen and 8.67 points (95% CI, 4.53 to 12.81) for external placebo, representing a LSM difference of -11.79 points (95% CI, -16.82 to -6.76), in favour of eplontersen. At week 66, the LSM change from baseline was -5.50 points (95% CI, -10.03 to -0.96) for eplontersen and 14.24 points (95% CI, 9.51 to 18.97) for external placebo, representing a LSM difference of -19.74 points (95% CI, -25.63 to -13.84), in favour of eplontersen. At both timepoints, the reduction in Norfolk QoL-DN scores corresponded to an improvement in HRQoL when treated with eplontersen.

Results for sensitivity analyses were consistent with the primary analysis, with point estimates for the LSM differences ranging from [redacted] at Week 35 and [redacted] at Week 65 [redacted] across sensitivity analyses.

The treatment effect of eplontersen on Norfolk QoL-DN total score across prespecified subgroups was consistent with the overall population, at the interim and final analyses.For the exploratory analysis of eplontersen and inotersen-eplontersen groups at Week 35, the mean change from baseline in Norfolk QoL-DN total score was -4.79 points (SD = 16.51) for eplontersen-treated patients (n = 130) and -2.97 points (SD = 12.10) following treatment with inotersen (n = 20).

Change from Baseline in COMPASS-31

The change from baseline in COMPASS-31 at Weeks 37 and 81 was an exploratory outcome of the NEURO-TTRansform study at the final analysis. COMPASS-31 was not assessed in the external placebo group. At baseline, the mean COMPASS-31 score in the eplontersen group was 19.4 points (SD = 11.26). The mean change from baseline at Weeks 37 and 81 were [redacted] and -2.6 points (SD = 7.52), respectively.

Change from Baseline of R-ODS

The change from baseline in R-ODS at Weeks 37 and 81 was an exploratory outcome of the NEURO-TTRansform study at the final analysis. [redacted] At baseline, the mean R-ODS score in the eplontersen group was [redacted] The mean change from baseline at Weeks 37 and 81 were [redacted] respectively.

Change from Baseline in Serum TTR

The change from baseline in serum TTR at Week 35 and Week 65 was a coprimary endpoint of the NEURO-TTRansform study. At the Week 35 interim analysis, the least squares mean (LSM) percent change from baseline in serum TTR was -81.20% (95% confidence interval [CI], -84.55 to -77.84) with eplontersen compared to -14.76% (95% CI, -18.73 to -10.80) for the external placebo group, representing a LSM difference of -66.43% (95% CI, -71.59, -61.71) in favour of eplontersen. At Week 65, the LSM percent change from baseline in serum TTR concentration was -81.65% [redacted] in the eplontersen group and -11.24% [redacted] in the external placebo group, representing a LSM difference of -70.42% [redacted], in favour of eplontersen. At both timepoints, the LSM difference corresponded to a reduction in serum TTR, or improvement in TTR levels for patients receiving eplontersen.

Results for all pre-specified sensitivity analyses of change from baseline in serum TTR at Week 65 were consistent with the primary analysis, as well as with Week 35, with point estimates for the LSM differences in percent reduction in serum TTR between eplontersen and external placebo ranging from [redacted]

In general, results of subgroup analyses were consistent at both analysis timepoints, and with the primary analysis. The subgroup of [redacted] LSM difference in percent reduction in serum TTR at Week 35 [redacted] and Week 65 [redacted]

For the exploratory analysis of eplontersen and inotersen-eplontersen groups at Week 35, the mean percent change from baseline in serum TTR was [redacted] for eplontersen-treated patients [redacted] and [redacted] following treatment with inotersen [redacted]

Change from Baseline in NSC Total Score

The change from baseline in neuropathy symptom and change (NSC) total score was a secondary outcome of the NEURO-TTRansform study at the final analysis. At Week 66, the LSM change from baseline was -0.03 points (95% CI, -1.92 to 1.86) in the eplontersen group and 8.2 points (95% CI, 6.24 to 10.12) in the external placebo group, representing a LSM difference of -8.2 points (95% CI, -10.65 to -5.76) in favour of eplontersen, corresponding to an improvement in neuropathy symptoms.

Change from Baseline in PCS Score of the SF-36

The change from baseline in the physical component summary (PCS) score of the 36-Item Short Form Survey (SF-36) was a secondary outcome of the NEURO-TTRansform study at the final analysis. At Week 65, the LSM change from baseline was 0.85 points (95% CI, -0.711 to 2.412) in the eplontersen group and -4.46 points (95% CI, -6.139 to -2.770) in the external placebo group, representing a LSM difference of 5.31 points (95% CI, 3.195 to 7.416), in favour of eplontersen, corresponding with an improvement in HRQoL with eplontersen.

Change from Baseline in PND Score

The change from baseline in PND score was a secondary outcome of the NEURO-TTRansform study at the final analysis. At Week 65, the LSM change from baseline was [redacted] in the eplontersen group and [redacted] in the external placebo group, representing a LSM difference of [redacted].

Hospitalizations

[redacted].

Harms Results

At the Week 66 final analysis, at least 1 treatment emergent adverse event (TEAE) was reported by 140 patients (97.2%) in the eplontersen group, and 60 patients (100%) in the external placebo group from the NEURO-TTR study. The most frequently reported TEAEs in the eplontersen group were COVID-19 (35 [24.3%]), urinary tract infection (24 [16.7%]), diarrhea (24 [16.7%]), vitamin A

deficiency (17 [11.8%]), and nausea (16 [11.1%]). The most frequently reported TEAEs in the external placebo group were fall (13 [21.7%]), fatigue (12 [20.0%]), diarrhea (11 [18.3%]), urinary tract infection (10 [16.7%]), neuralgia (9 [15.0%]), pain in extremity, cough, asthenia, pain (8 [13.3%] each), nausea, headache (7 [11.7%] each), and nasopharyngitis, dizziness, constipation, thermal burn, hypoesthesia, and muscular weakness (6 [10.0%] each).

Serious adverse events (SAEs) were reported in 21 patients (14.6%) in the eplontersen group and 12 patients (20.0%) in the external placebo group. The most reported individual SAEs in the eplontersen group were [redacted] The most reported SAEs in the placebo group included [redacted]

TEAEs leading to discontinuation of treatment occurred in 6 patients (4.2%) in the eplontersen group and 2 patients (3.3%) in the external placebo group.

Up to Week 66, 2 patients in the eplontersen group had died; one due to arrhythmia, and the other due to cerebral hemorrhage. Between Week 66 and week 85, one additional patient in the eplontersen group had died due to myocardial infarction. At the week 66 analysis, no patients in the external placebo group had died.

Notable harms included in this review consisted of ocular AEs potentially related to vitamin A deficiency, and thrombocytopenia. In the eplontersen group, [redacted], however, since investigators in the NEURO-TTR study were blinded to vitamin A levels so as not to inadvertently be unblinded to treatment allocation, no vitamin A-related AEs were reported. The most common ocular AEs potentially related to [redacted] For thrombocytopenia, a total of 3 AEs (2.1%) were reported in the eplontersen group, and 1 (1.7%) was reported in the external placebo group at Week 66.

Critical Appraisal

The NEURO-TTRansform study was a randomized, open-label study that utilized an external placebo control from the NEURO-TTR study of inotersen compared to placebo. The choice to conduct a study using external control has implications for the overall strength and interpretability of the results. The design, study sites, eligibility criteria, and assessments of disease progression of the NEURO-TTRansform study and NEURO-TTR study were aligned for the purpose of this comparison. As the NEURO-TTRansform study was an open-label study, there was an increased risk of detection bias and performance bias, particularly for subjective outcomes, though the magnitude and direction of this bias remains unclear. Despite randomization, no statistical comparisons were conducted comparing eplontersen with the concurrent inotersen arm for randomized patients, rather was only conducted for safety comparisons, and considering the large sample size that would have been required, which the sponsor considered to be infeasible for this rare indication. The baseline characteristics were fairly balanced, with the exception of some baseline scores (i.e., mNIS+7 and neuropathy impairment score (NIS) composite scores, and PND scores), which were generally higher in the eplontersen group, suggesting a population with more severe neuropathy impairment compared to those enrolled in the inotersen-eplontersen group. In comparison to the external placebo group from the NEURO-TTR study, the NEURO-TTRansform study included younger patients, had a greater proportion of Asian, and Black patients, included more patients with FAP and/or Coutinho stage 1 disease but fewer with stage 2, had a longer period of time from diagnosis to enrollment, included fewer patients with CM, and more patients with previous experience with tafamidis or diflusinal. The impact of these differences on the results remains unknown, though subgroup analyses for these variables were generally consistent with the primary results. The NEURO-TTRansform study met its co-primary and key secondary endpoints at the interim analysis, and therefore further statistical testing was not conducted on these endpoints at the final analysis. Results at the final analysis were consistent with the interim analysis across all study endpoints, despite the switch from ANCOVA at the interim analysis to MMRM at week the final analysis for endpoints of change from baseline in mNIS+7 and change from baseline in Norfolk QoL-DN. Given the use of the external placebo control, the mixed model for repeated measures (MMRM) for each endpoint was adjusted by propensity score weights for each patient. It was unclear how the covariates for adjustment were selected, or whether all relevant prognostic factors and effect modifiers were considered. Additionally, it was not possible to account for differences in known unmeasured or unknown confounders. As such, there is a risk of bias due to residual baseline confounding of unknown magnitude and direction.

The NEURO-TTRansform trial was an international trial conducted in 15 countries, including Canada, which enrolled 3 patients. Patients eligible for the NEURO-TTRansform study were similar to those eligible for the NEURO-TTR study given the identical eligibility criteria. Similar to other treatments for hATTR-PN, the NEURO-TTRansform study enrolled adult patients with stage 1 or stage 2 PN with hATTR. Patients receiving current or prior treatment with TTR-lowering treatment were excluded from the NEURO-TTRansform trial. As such, the efficacy of eplontersen in patients who previously received patisiran or vutrisiran is unknown.

The clinical experts consulted for this review also highlighted there is limited overlap in outcomes between clinical trials for hATTR-PN and clinical practice, emphasizing that many of the measures included as outcomes in the NEURO-TTRansform trial are not routinely used in Canadian clinical practice. The primary endpoint of the NEURO-TTRansform study was the percent change from baseline in serum TTR. The abnormal aggregation of TTR is a fundamental manifestation of hATTR-PN, however, the clinical experts noted that serum TTR levels are not measured routinely in clinical practice. Though demonstrative of treatment effect and biological plausibility, serum TTR reduction has not been identified as a validated surrogate outcome for efficacy in hATTR-PN, thus its use as primary endpoint may have been inappropriate. The mNIS+7 and Norfolk QoL-DN measures have limited application in clinical practice in Canada given the complexity and time-consuming nature of these tools. The clinical experts noted that COMPASS-31, R-ODS, and other tools (ONLS and mTCNS) are more frequently used given their simplicity, though it is not standardized across Canada. COMPASS-31 and R-ODS were exploratory outcomes of the NEURO-TTRansform study though did not include a comparison to placebo, and should only be considered supportive, while the ONLS and modified Toronto Clinical Neuropathy Score (mTCNS) were not reported in the NEURO-TTRansform study.

GRADE Summary of Findings and Certainty of the Evidence

For pivotal studies and RCTs identified in the sponsor's systematic review, GRADE was used to assess the certainty of the evidence for outcomes considered most relevant to inform CADTH's expert committee deliberations, and a final certainty rating was determined as outlined by the GRADE Working Group. For the comparison of eplontersen to placebo, which leveraged an external placebo group from NEURO-TTR, the certainty of evidence started at low, acknowledging the non-randomized design and risk for selection bias and residual baseline confounding. The clinical review team assessed the submitted evidence for study limitations (i.e., internal validity or risk of bias), indirectness, imprecision of effects, and publication bias. In the absence of a comparator (i.e., single arm design), appraisals of the results for COMPASS-31 and R-ODS started at very low certainty with no opportunity for rating up.

The selection of outcomes for GRADE assessment was based on the sponsor's Summary of Clinical Evidence, consultation with clinical experts, and input received from patient and clinician groups and public drug plans. The following list of outcomes was finalized in consultation with expert committee members: serum TTR levels, mNIS+7 composite score, Norfolk QoL-DN total score, COMPASS-31, R-ODS, ocular AEs potentially related to vitamin A deficiency, and thrombocytopenia.

When possible, certainty was rated in the context of the presence of an important (nontrivial) treatment effect; if this was not possible, certainty was rated in the context of the presence of any treatment effect (i.e., the clinical importance is unclear). In all cases, the target of the certainty of evidence assessment was based on the point estimate and where it was located relative to the threshold for a clinically important effect (when a threshold was available) or to the null. The target of the certainty of evidence assessment was the presence or absence of any effect for serum TTR, mNIS+7 composite score, and Norfolk QoL-DN total score.

Table 3 presents the GRADE summary of findings for eplontersen vs. placebo for outcomes in the pivotal NEURO-TTRansform trial.

Table 3: Summary of Findings for Eplontersen Versus Placebo (NEURO-TTR) for Patients With hATTR-PN in the NEURO-TTRansform Trial

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty[a]	What happens
			Placebo (NEURO-TTR)	Eplontersen (NEURO-TTRansform)	Difference		
Neuropathy Symptoms and Neurologic Function							
mNIS+7 composite score (-22.3 [best] to 346.3 [worst] points) LSM change from baseline Follow-up: Week 35	199 (1 non-randomized study)	NA	9.23	0.22 (-3.46, 3.90)	-9.01 (-13.48, -4.54)	Low[b, c, d]	Eplontersen may result in lesser neurological impairment based on the change from baseline in mNIS+7 composite score compared to placebo.
mNIS+7 composite score (-22.3 [best] to 346.3 [worst] points) LSM change from baseline Follow-up: Week 66	180 (1 non-randomized study)	NA	25.06	0.30 (-4.46, 5.06)	-24.76 (-30.96, -18.56)	Low[b, d]	Eplontersen may result in lesser neurological impairment based on the change from baseline in mNIS+7 composite score compared to placebo.
COMPASS-31 score (0 [best] to 100 [worst]), Mean (SD) change from baseline Follow up: Weeks 37 and 81	141 (1 single-arm study)	NA	NA	• [redacted]	NA	Very low[a, e]	The evidence is uncertain about the effect of eplontersen on COMPASS-31 scores when compared with any comparator.
R-ODS score (0 [worst] to 48 [best]), Mean (SD) change from baseline Follow up: Weeks 37 and 81	141 (1 single-arm study)	NA	NA	• [redacted]	NA	Very low[a, e]	The evidence is uncertain about the effect of eplontersen on R-ODS scores when compared with any comparator.
Health-related Quality of Life							
Norfolk QoL-DN total score (-4 [best] to 136 [worst]), LSM	191 (1 non-randomized study)	NA	8.67	-3.12 (-7.19, 0.96)	-11.79 (-16.82, -6.76)	Low[b, c, f]	Eplontersen may result in better HRQoL based on the change from baseline in

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty[a]	What happens
			Placebo (NEURO-TTR)	Eplontersen (NEURO-TTRansform)	Difference		
change from baseline Follow-up: Week 35							Norfolk QoL-DN total score compared to placebo.
Norfolk QoL-DN total score (-4 [best] to 136 [worst]), LSM change from baseline Follow-up: Week 66	180 (1 non-randomized study)	NA	14.24	-5.50 (-10.03, -0.96)	-19.74 (-25.63, -13.84)	Low[b, f]	Eplontersen may result in better HRQoL based on the change from baseline in Norfolk QoL-DN total score compared to placebo.
Serum TTR							
Percent change from baseline in Serum TTR, LSM Follow-up: Week 35	193 (1 non-randomized study)	NA	-14.76	-81.20 (-84.55, -77.84)	-66.43 (-71.39, -61.47)	Moderate[c, g]	Eplontersen likely results in an increase (improvement) in serum TTR levels when compared with placebo.
Percent change from baseline in Serum TTR, LSM Follow-up: Week 65	186 (1 non-randomized study)	NA	-11.24	-81.65 (-84.82, -78.48)	-70.42 (-75.17, -65.66)	Moderate[g]	Eplontersen likely results in an increase (improvement) in serum TTR levels when compared with placebo.
Notable Harms							
Ocular AEs potentially related to Vitamin A deficiency Follow-up: Week 66	204 (1 non-randomized study)	NR	150 per 1,000	271 per 1,000 (NR)	NR	Very low[b, h, i]	The evidence is uncertain about the effect of eplontersen on ocular AEs when compared with placebo.
Thrombocytopenia Follow-up: Week 66	204 (1 non-randomized study)	NR	17 per 1,000	21 per 1,000 (NR)	NR	Very low[b, h]	The evidence is uncertain about the effect of eplontersen on thrombocytopenia when compared with placebo.

AE = adverse event; CI = confidence interval; COMPASS-31 = Composite Autonomic Symptom Score-31; NA = not applicable; NR = not reported; RCT = randomized controlled trial; R-ODS = Rasch-built Overall Disability Score; SD = standard deviation; TTR = transthyretin.

Note: Study limitations (which refer to internal validity or risk of bias), indirectness, imprecision of effects, and publication bias were considered when assessing the certainty of the evidence. All serious concerns in these domains that led to the rating down of the level of certainty are documented in the table footnotes.

[a] The NEURO-TTRansform study used an external control (placebo group in the NEURO-TTR trial) for comparison with the eplontersen group. This observational comparison introduced potential for bias, resulting from confounding and selection bias, and the certainty of evidence was started at low. The clinical review team noted that the external placebo control was collected from a randomized, double-blind, placebo-controlled study (NEURO-TTR) that was conducted using the same eligibility criteria and disease assessments as the NEURO-TTRansform study. However, the risk of bias due to residual baseline confounding could not be ruled out. Results for the change from baseline in COMPASS-31 and R-ODS scores lacked a comparator and were started at very low certainty without the opportunity to be rated up.

[b] Although there is a risk of bias arising from the open-label nature of the study and the subjective nature of the outcome, the certainty of evidence was not rated down. Starting the certainty of evidence at low already acknowledges the serious risk of study limitations.

[c] Potential to be rated down 1 level for serious internal validity limitations as results at Week 35 are based on an interim analysis. The review team assessed the interim analyses for the potential to overestimate treatment effects; however, it was concluded that the risk of serious study limitations is not a concern because the results of the interim analysis were aligned with the results of the final analysis. As such, the certainty was not rated down.

[d] Imprecision was not rated down. Per the clinical experts consulted for this review, any stabilization or decrease in mNIS+7 score from baseline is viewed positively, however, were unable to provide a threshold of clinically meaningful improvement. As such, the clinical review team used the null as the threshold. The lower bound of the 95% CIs excluded the null.

[e] End point was an exploratory outcome without statistical testing, and the findings should be considered as supportive evidence.

[f] Imprecision was not rated down. No threshold of clinical importance was provided by the clinical experts consulted for this review. As such, the null was used as a threshold. The lower bound of the 95% CIs exceeded the null.

[g] The certainty of evidence was starting at low, acknowledging the potential for residual baseline confounding and selection bias as a result of the non-randomized study design. The certainty of evidence was rated up by 1 level to account for the large effect size, which is biologically plausible and aligned with the mechanism of action of eplontersen. Note that serum TTR is considered a biomarker for efficacy of treatment in patients with hATTR-PN, however, the validity of its relationship as a surrogate for clinical outcomes has not been established.

[h] Rated down 1 level for serious imprecision due to the low number of events and small sample size.

[i] This outcome was not measured the same way in both trials. In the NEURO-TTR study, investigators were blinded to vitamin A levels so as not to inadvertently be unblinded to Study Drug allocation. As such, vitamin A-related AEs were not reported in this study.

Source: NEURO-TTRansform Clinical Study Report Interim and Final Analyses (2023)

Long-Term Extension Studies

One open-label extension study of patients with hATTR-PN who are continuing to receive eplontersen after week 85 in NEURO-TTRansform is currently ongoing. No data were available at the time this review.

Indirect Comparisons

Description of Studies

Given the lack of head-to-head studies comparing the efficacy and/or safety of eplontersen to other treatments available in Canada (i.e., vutrisiran, patisiran, and inotersen) for hATTR-PN, the sponsor submitted an indirect treatment comparison (ITC) to evaluate the comparative efficacy of eplontersen versus other medical therapies used for the treatment of patients with hATTR-PN.

The sponsor conducted an unanchored matching adjusted indirect comparison (MAIC) and simulated treatment comparison (STC) comparing eplontersen from the NEURO-TTRansform study to inotersen from the NEURO-TTR trial, patisiran form the APOLLO and HELIOS-A trials, and vutrisiran from the HELIOS-A trial for the outcomes of change from baseline in mNIS+7, change from baseline in Norfolk QoL-DN, and percent change from baseline in serum TTR.

Efficacy Results

For the change from baseline in mNIS+7, there were no statistically significant differences detected between eplontersen and vutrisiran from the HELIOS-A trial, patisiran from the HELIOS-A trial, or inotersen from the NEURO-TTR trial. [redacted] In the alternative models, there were no statistically significant differences detected between eplontersen and vutrisiran from the HELIOS-A trial, or patisiran from the HELIOS-A trial, but resulted in a statistically significant improvement in mNIS+7 composite score compared to inotersen [redacted]

For the change from baseline in Norfolk QoL-DN, comparisons of eplontersen to vutrisiran from the HELIOS-A trial, and inotersen from the NEURO-TTR trial demonstrated a statistically significant improvement in Norfolk QoL-DN total score from [redacted]

For the change from baseline in serum TTR concentration, [redacted] and eplontersen and inotersen from the NEURO-TTR trial demonstrated statistically significant reductions in serum TTR concentration [redacted], in favour of eplontersen, which suggested that eplontersen results in greater reductions in serum TTR levels. However, there was no statistically significant difference detected between eplontersen and vutrisiran. Results for the alternative model were generally consistent with the reference model, however, [redacted] Percent change from baseline in serum TTR concentration was not evaluated in the comparison between eplontersen and patisiran from the APOLLO trial.

Critical Appraisal

The sponsor-submitted MAIC and STCs were informed by an adequately conducted systematic literature review (SLR) that included planned searches of multiple databases, and standard screening and extraction methods. Risk of bias assessments of the included studies were conducted per the University of York Centre for Reviews and Dissemination criteria, however, the results of this quality assessment were not provided, thus, the potential impact of study-level biases on the results of the MAICs and STCs could not be comprehensively judged.

In total, 4 trials evaluating eplontersen, vutrisiran, patisiran, and inotersen were identified for inclusion during the sponsors feasibility assessment. Given the heterogeneity observed, the lack of a common comparator across the included trials, and the unique design of two studies that included randomized reference arms (NEURO-TTRansform [inotersen arm] and HELIOS-A [patisiran arm] studies), the sponsor concluded that MAIC and STC methods were most appropriate for comparing eplontersen and relevant comparators. Other sources of heterogeneity in the included studies were baseline characteristics of age, proportion of patients who identify as white, proportion of patients with V30M mutation, proportion of patients with hATTR with CM, proportion of patients with previous treatment with tafamidis or diflusinal, proportion of patients with Stage 1 and Stage 2 disease, as well as differences in various outcome scores.

In the base case (reference) models, comparisons of eplontersen to other treatments resulted in sample size decreases of [redacted] across outcomes and treatments. Sample size decreases were generally smaller in the alternative models, as fewer variables were included in the adjustment. Given the reduction in ESS, there was likely considerable heterogeneity between studies among the variables included in the weighting process. Despite the substantial reduction in ESS for nearly all comparisons following the matching and adjustment, the populations in all MAIC and STC analyses were relatively balanced. Substantial reductions in ESS have implications for generalizability and the precision of effect estimates. A comprehensive list of prognostic factors and treatment-effect modifiers was included and based on discussions with the clinical experts consulted by for this review, were considered relevant. However, it was noted that the exclusion of region as a factor may bias the results as there may be regional variation in healthcare access and treatment approaches that are unrelated to V30M.

Two versions of the mNIS+7 were utilized in the analyses (mNIS+7$_{Ionis}$ and mNIS+7$_{Alnylam}$ composite scores). The mNIS+7$_{Ionis}$ composite score from NEURO-TTRansform study was rescored, however, the rescored versions are not validated for use and may not be appropriate given that certain domains are not captured within the rescored version. Thus, any interpretation of the comparative results for the mNIS+7 composite score should consider this limitation. Additionally, outcomes for the mNIS+7 composite score and Norfolk-QoL-DN total score were extrapolated to match the timepoints reported in the comparator trial, which may introduce uncertainty into the magnitude of any estimates of treatment effect. In the reference model, for the outcome of mNIS+7, there was generally insufficient evidence to determine whether eplontersen or the comparator treatments were favoured given the wide 95% CIs that included the potential for stabilization of disease, as well as the potential for disease progression. For the Norfolk QoL-DN and change from baseline in serum TTR outcomes, eplontersen was often favoured over other treatments, though imprecision and uncertainty remained given the wide 95% CIs.

Studies Addressing Gaps in the Evidence from the Systematic Review

No studies addressing gaps in the systematic review evidence were submitted by the sponsor.

Economic Evidence

Cost and Cost-Effectiveness

Table 4: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Markov Model
Target population	Adults with hereditary transthyretin-mediated amyloidosis polyneuropathy (hATTR-PN)
Treatment	Eplontersen
Dose regimen	45 mg once per month
Submitted price	$47,680.33 per pre-filled single-dose pen
Submitted treatment cost	$572,164 per patient per year
Comparators	• Inotersen • Patisiran

Component	Description
	• Vutrisiran
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (47 years)
Key data source	Efficacy of eplontersen informed by the NEURO-TTRansform study. Efficacy of comparators informed by unanchored matching adjusted indirect comparisons (MAICs).
Key limitations	• It is uncertain whether eplontersen provides a clinical benefit relative to vutrisiran, patisiran, or inotersen for hATTR-PN due to limitations in the clinical evidence submitted by the sponsor. There have been no head-to-head trials of eplontersen to comparators, and the CADTH clinical review concluded that the submitted indirect treatment comparisons were insufficient to determine whether eplontersen would be associated with different clinical outcomes relative to comparators, owing to methodological limitations. • The validity of using Norfolk QoL-DN scores to estimate disease progression via Coutinho Stages is uncertain based on clinical expert feedback. It is highly uncertain whether Norfolk QoL-DN scores can be used to define Coutinho stages, whether the Norfolk QoL-DN cut-offs for defining disease stages used in the model are appropriate, and whether changes in Norfolk QoL-DN score appropriately capture disease progression. Change in Coutinho stage was not assessed in the NEURO-TTRansform study. • The methods used by the sponsor to estimate transitions between model health states were overly complex and introduced considerable uncertainty. These methods relied on the creation of pseudo individual patient data for comparators, the use of regression models to adjust for the timing of outcome assessment, and assumptions that were not verifiable by CADTH. • The sponsor's model lacked transparency, which prevented CADTH from verifying the underlying data calculations. • The long-term efficacy of eplontersen is uncertain owing to a lack of clinical data beyond 85 weeks. Potential waning of effectiveness was not explored. • The impact of adverse events on the cost-effectiveness of eplontersen was based on naïve comparison and it is not possible to determine if any differences between the therapies are solely due to the treatment or, rather, due to bias or confounding factors. Outcomes considered important by clinicians (vitamin A deficiency-related consequences; thrombocytopenia) and patients (falls) were not included in the sponsor's model. Falls were reported by 5.6% of patients in the eplontersen group in the TTRansform trial, while the incidence of vitamin A deficiency and thrombocytopenia SAEs was less than 2%.
CADTH reanalysis results	• CADTH was unable to address uncertainty in the comparative clinical evidence or identified limitations in the submitted economic evaluation. A CADTH base case could therefore could not be specified. • There is insufficient evidence to justify a price premium for eplontersen over currently available treatments for hATTR-PN. Thus, eplontersen should be priced no more than the lowest cost treatment used to treat hATTR-PN that is funded.

hATTR-PN = hereditary transthyretin-mediated amyloidosis polyneuropathy; ICER = incremental cost-effectiveness ratio; LY = life-year; QALY= quality-adjusted life-year; QoL = quality of life; DN = diabetic neuropathy; SAE = serious adverse events.

Budget Impact

CADTH identified the following limitations in the sponsor's base case: uncertainty in the number of patients with hATTR-PN, and uncertainty in the prices paid by public drug plans is uncertain. In the absence of more reliable estimates to inform the parameters of the BIA, the sponsor's base case was maintained. The budget impact from the introduction of eplontersen was estimated to be $51,177 in Year 1, $390,203 in Year 2, and $430,199 in Year 3, for a 3-year incremental cost of $871,579.

CDEC Information

Members of the Committee:

Dr. James Silvius (Chair), Dr. Sally Bean, Mr. Dan Dunsky, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Trudy Huyghebaert, Dr. Peter Jamieson, Mr. Morris Joseph, Dr. Christine Leong, Dr. Kerry Mansell, Dr. Alicia McCallum, Dr. Srinivas Murthy, Dr. Danyaal Raza, Dr. Edward Xie, and Dr. Peter Zed.

Meeting date: August 28, 2024

Regrets:

2 expert committee members did not attend.

Conflicts of interest:

None