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Reimbursement Recommendation

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.

Final recommendation: Reimburse with conditions

Summary

What Is the Reimbursement Recommendation for Wainua?

Canada's Drug Agency (CDA-AMC) recommends that Wainua be reimbursed by public drug plans for the treatment of polyneuropathy (PN) associated with stage I or stage II hereditary transthyretin amyloidosis (hATTR) in adults, if certain conditions are met.

Which Patients Are Eligible for Coverage?

Wainua should only be covered to treat adults with stage I or stage II genetically confirmed hATTR with PN (hATTR-PN) who are symptomatic with early-stage neuropathy, do not have severe heart failure symptoms, and have not had a liver transplant. A patient's response to treatment with Wainua should be assessed at least every 6 months to determine whether they would benefit from continued treatment. Treatment with Wainua should not be continued in patients who are permanently bedridden and dependent on assistance for basic activities of daily living or who are receiving end-of-life care.

What Are the Conditions for Reimbursement?

Wainua should only be reimbursed if the patient is under the care of a specialist with experience in the diagnosis and management of hATTR-PN, and should not be reimbursed if it is used in combination with interfering ribonucleic acid (RNA) drugs or transthyretin stabilizers. The cost of Wainua should be reduced so that it does not cost more than other drugs for hATTR.

Why Did We Make This Recommendation?

- Evidence from a clinical trial demonstrated that, in patients with hATTR-PN, treatment with Wainua reduces TTR protein production and improves neuropathy-related neurologic function and health-related quality of life (HRQoL), as measured by modified Neuropathy Impairment Score plus 7 (mNIS+7) score and Norfolk Quality of Life questionnaire – Diabetic Neuropathy (QoL-DN) score, when compared to treatment with placebo.
- Wainua may meet some needs that are important to patients because it provides another subcutaneous (SC) drug option that can be administered in a patient's home, which addresses a need identified by patients.
- Based on our assessment of the health economic evidence, Wainua does not represent good value to the health care system at the public

Summary

list price. The committee determined that there is not enough evidence to justify a greater cost for Wainua compared with currently available treatments for hATTR-PN.

- Based on public list prices, Wainua is estimated to cost the public drug plans approximately $800,000 over the next 3 years; however, the actual budget impact is uncertain.

Additional Information

What Is hATTR-PN?

hATTR is an inherited condition caused by alterations in a gene that makes a protein called TTR, and results in the misfolding of the TTR protein. In people with hATTR, this misfolded protein forms into abnormal fibrous tissue called amyloids, which can build up in the body's organs and peripheral nerves causing organs to not function properly as well as nerve damage. In patients with hATTR-PN, amyloids primarily build up in the peripheral nerves. hATTR is considered a rare disease, affecting about 10,000 people worldwide.

Unmet Needs in hATTR-PN

Patients with hATTR-PN need effective treatments that slow disease progression, have a low risk of adverse events (AEs), improve HRQoL, improve convenience and independence, and have less frequent dosing.

How Much Does Wainua Cost?

Treatment with Wainua is expected to cost approximately $572,164 per patient per year.

Recommendation

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

Rationale for the Recommendation

One phase III, randomized, open-label trial (the NEURO-TTRansform trial) in adults with hATTR-PN demonstrated that, compared with an external placebo group (from the NEURO-TTR study), treatment with eplontersen resulted in an improvement in neurologic function as measured by the (mNIS+7) (least squares mean difference [LSMD] at week 66 = −24.76 points; 95% confidence interval [CI], −30.96 to −18.56) and HRQoL as measured by the Norfolk QoL-DN (LSMD at week 66 = −19.74 points; 95%CI, –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 (MAICs), 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, require less frequent dosing, halt disease progression, and improve 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 SC drug option that can be administered in a patient's home; however, it was unknown whether the potential at-home administration method with a prefilled pen is less burdensome for patients and improves HRQoL relative to administration by a health care provider for other treatments, as this was not explicitly studied. CDEC also highlighted that compared to placebo, HRQoL and neurologic function remained stable, although 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. Treatment with eplontersen should be reimbursed in adult patients with stage I or stage II genetically confirmed hATTR-PN who are symptomatic with early-stage neuropathy, defined as: 1.1. PND stage I to ≤ IIIB, or FAP stage I or II 1.2. no severe heart failure symptoms (defined as NYHA class III or IV) 1.3. no previous liver transplant.	In the NEURO-TTRansform trial, eplontersen demonstrated clinically meaningful benefits for patients with stage I or stage II hATTR-PN when compared to an external placebo control group. Patients with advanced polyneuropathy (i.e., PND stage IV or FAP stage III), and prior liver transplant were excluded from the NEURO-TTRansform trial; therefore, there is no evidence to support the use of eplontersen in these patients.	Genetic testing is required to confirm a diagnosis of hATTR to differentiate this condition from other causes of amyloidosis.
Renewal		
2. An initial clinical assessment of treatment response should occur 9 months after treatment initiation. Thereafter, patients should be assessed at least every 6 months to determine whether they would benefit from continued treatment with eplontersen.	According to the clinical experts, patients' overall functioning, quality of life, and ability to perform daily activities are determined through comprehensive clinical history. Continuous clinical assessments ensure accurate monitoring of the patient's response to treatment. Timing of assessments depends on the severity of a patient's disease; in more active patients, assessment every 3 or 6 months is appropriate.	—
Discontinuation		
3. Treatment with eplontersen should be discontinued for patients who are: 3.1. permanently bedridden and dependent on assistance for basic activities of daily living, or 3.2. receiving end-of-life care.	No evidence was identified to demonstrate that continuing treatment with eplontersen in patients whose disease has progressed is effective.	—
Prescribing		
4. The patient must be under the care of a specialist with experience in the diagnosis and management of hATTR-PN.	This is meant to ensure that eplontersen is prescribed only for appropriate patients and adverse effects are managed in an optimized and timely manner.	—
5. Eplontersen should not be used in combination with other interfering RNA drugs or transthyretin stabilizers used to treat hATTR.	There are no data supporting the efficacy and safety of eplontersen when used in combination with other interfering RNA drugs or transthyretin stabilizers.	—

Reimbursement condition	Reason	Implementation guidance
Pricing		
6. The price of 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.	—

FAP = familial amyloidotic polyneuropathy; hATTR = hereditary transthyretin amyloidosis; PN = polyneuropathy; NYHA = New York Heart Association; PND = polyneuropathy disability; RNA = ribonucleic acid.

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 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 neurologic 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 Grading for Recommendations Assessment, Development and Evaluation (GRADE) approach (moderate certainty for serum TTR levels), generally related to the study design and the lack of minimally clinical important difference thresholds, which reduced the certainty of evidence for eplontersen relative to placebo. CDEC also noted 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, which the clinical experts consulted for this review noted 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 (Composite Autonomic Symptom Score 31 [COMPASS-31] and Rasch-Built Overall Disability Scale [R-ODS]), which were exploratory and noncomparative in the NEURO-TTRansform study and 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 SC 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 assessed 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 and relatively small sample size of the NEURO-TTRansform study, 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 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 MAIC that compared eplontersen to vutrisiran, patisiran, and inotersen. However, numerous limitations in the analyses (including small sample sizes as well as heterogeneity across study designs and populations), in addition to 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 is higher than estimated, the budget impact of reimbursing eplontersen will be greater.
- Following feedback on the draft recommendation received from sponsor and drug programs, Table 1 was updated to align with the conditions included in the CDEC recommendation for vutrisiran rather than the criteria used by each of the public drug plans for vutrisiran, as vutrisiran was not listed in Canada when this recommendation was published.

Background

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. 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 cardiac system are heavily affected, leading to 2 of the primary manifestations of the disease: polyneuropathy (PN) and cardiomyopathy (CM).

Clinically, hATTR often progresses rapidly and leads to worsening sensorimotor neuropathy, a condition that damages an individual's sensory and motor nerves, escalating their 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 hATTR-PN is assessed and classified using 2 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 onset (i.e., in patients younger than 50 years) or late onset (i.e., in patients aged 50 years or older), although there is significant worldwide variability regarding age of onset. The life expectancy of patients with hATTR-PN ranges from 10 to 15 years following initial symptom onset.[4] The median survival from the time of diagnosis of hATTR-PN is 4.7 years.

hATTR-PN is an ultra-rare disease affecting approximately 10,000 individuals worldwide, although 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 2 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, biomarker measurement, and cardiac evaluation.

There have been 2 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 CDA-AMC for the treatment of stage I or stage II PN in adult patients with hATTR.

Eplontersen has been approved by Health Canada for the treatment of PN associated with stage I or stage II 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 prefilled pen for SC 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 III randomized, open-label study in patients with hATTR and 2 indirect treatment comparisons (ITCs)
- patients' perspectives gathered by 1 patient group, Transthyretin Amyloidosis Canada (TAC)
- input from public drug plans that participate in the CDA-AMC 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.

Perspectives of Patients, Clinicians, and Drug Programs

Patient Input

One patient group submitted input for this submission: TAC, a not-for-profit organization which supports individuals living with all forms of transthyretin amyloidosis, including hATTR and wild-type transthyretin amyloidosis, 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 older than 65 years.

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 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, multisystem 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 had 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 fewer 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 had a significant impact on their ability to maintain their social life, indicating that their identity was engrossed in their disease, 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 CDA-AMC

The clinical experts shared that currently, there are no therapies available that can reverse neuropathy in hATTR. The primary aim of existing treatments for 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 AEs with inotersen and a 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 health care 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 autoinjector or orally.

Since the approval of disease-modifying therapy, patients with hATTR-PN in Canada receive 1 of either inotersen, patisiran, or vutrisiran (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 for this review, eplontersen would be used similarly to other first-line treatment options (inotersen, patisiran, or vutrisiran) and a 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, although 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 transplant. 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 favourably 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, although 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 fibres 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 eplontersen 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., those who are physically unable to leave bed) 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 centres may use patient-reported outcomes to follow patients, but this is not standardized across Canada. Nerve conduction studies and small fibre assessments to evaluate large and small fibre function may be conducted. Other nonstandardized assessments include autonomic function tests to gauge patient experiences, such as the COMPASS-31 scale; and track neuropathy severity with the Toronto Clinical Neuropathy scale (TCNS), Overall Neuropathy Limitation Scale (ONLS), and 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 fibre neuropathies, and 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 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, mortality, and reduced QoL. The NMD4C stated that patients in the early stages of disease (stage I or II 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 1 treatment indicates that failure of a different treatment would occur; thus, having multiple treatment options available is important. While it was not the first drug approved, the NMD4C provided their opinion that 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 neurologic history, neurologic 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 experiencing a response 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 centres with lines of referral to cardiologists. The NMD4C also highlighted that hospital outpatient neuromuscular clinics, and community-based neurologic clinics and referral lines to neuromuscular expertise may also be appropriate.

Drug Program Input

The clinical experts consulted by CDA-AMC 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 III, multicentre, 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. Vutrisiran, 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 I or stage II 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 end points 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	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
severity, ranging from every 3 to 6 months or more. With no clearly defined renewal criteria for patisiran, inotersen, or vutrisiran, consistency with currently used approaches for monitoring in clinical practice settings would be reasonable. 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 neurologic 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 RNA 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, because 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 time frame or other factor to indicate when this switch may occur? Under what conditions would it be appropriate to switch from inotersen, patisiran, or vutrisiran to eplontersen?	The clinical experts noted that patients may choose to switch treatments for various reasons (AEs, dosing schedule, patient preference, and so forth), but was noted by both CDEC and the clinical experts that there is currently no evidence supporting switching from inotersen, patisiran, or vutrisiran 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.

Implementation issues	Response
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.
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 reimbursement 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.

Clinical Evidence

Systematic Review

Description of Studies

One study was included in this review. The NEURO-TTRansform study was an 85-week, phase III, 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 then switched to eplontersen (inotersen-eplontersen) SC once every 4 weeks from week 37 to week 81 (n = 24). The NEURO-TTRansform study was conducted at 40 sites in 15 countries (in Asia, Australasia, Europe, North America, and South America), including 2 sites in Canada (British Columbia and Ontario) that enrolled 3 patients. There were 3 analysis time points in the NEURO-TTRansform study: week 35 (interim analysis), week 65 to week 66 (final analysis), and week 85 (end of treatment analysis). Three co-primary end points were used at the final analysis: the percent change from baseline in serum TTR, change from baseline in mNIS+7, and change from baseline in Norfolk QoL-DN.

The NEURO-TTRansform study also included an external control group using the placebo arm (n = 60) from the NEURO-TTR study. The NEURO-TTR study 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

I or II 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 in the NEURO-TTRansform study and the external placebo group in 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 the NEURO-TTRansform study, most patients had stage I hATTR-PN (115 [79.9%]), as well as V30M mutations (85 [59.0%]), while in the NEURO-TTR placebo group, 42 patients (70.0%) had stage I hATTR-PN and 33 (55.0%) had V30M mutations. In the 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 co-primary end point of the NEURO-TTRansform study at the interim and final analyses. At week 35, the least squares mean (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 an LSMD 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 LSMD of −24.76 points (95% CI, −30.96 to −18.56) in favour of eplontersen. At both time points, the reduction in mNIS+7 scores corresponded to an improvement in the severity of neuropathy when treated with eplontersen.

Results for the prespecified sensitivity analyses were consistent at the interim and final analyses and with the primary analysis, with point estimates for the LSMDs 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 patients treated with eplontersen (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 end point of the NEURO-TTRansform study at the week 35 interim analysis and a co-primary end point 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 an LSMD 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 LSMD of −19.74 points (95% CI, −25.63 to −13.84) in favour of eplontersen. At both time points, the reduction in Norfolk QoL-DN scores corresponded to an improvement in HRQoL when patients were treated with eplontersen.

Results for sensitivity analyses were consistent with the primary analysis, with point estimates for the LSMDs 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 patients treated with eplontersen (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 in 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 co-primary end point of the NEURO-TTRansform study. At the week 35 interim analysis, the LSM percent change from baseline in serum TTR was −81.20% (95% 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 LSMD 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 an LSMD of −70.42% [redacted] in favour of eplontersen. At both time points, the LSMD corresponded to a reduction in serum TTR, or improvement in TTR levels for patients receiving eplontersen.

Results for all prespecified 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 LSMDs 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 time points, and with the primary analysis. The subgroup of [redacted] LSMD 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 patients treated with eplontersen [redacted] and [redacted] following treatment with inotersen [redacted]

Change From Baseline in Neuropathy Symptom and Change 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 an LSMD 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 Physical Component Summary Score of the SF-36

The change from baseline in the physical component summary (PCS) score of the Short Form (36) Health 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 an LSMD 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 an LSMD of [redacted].

Hospitalizations

[redacted]

[redacted] | | [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: 1 due to arrhythmia, and the other due to cerebral hemorrhage. Between week 66 and week 85, 1 additional patient in the eplontersen group 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, although 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 I disease but fewer with stage II disease, had a longer period of time from diagnosis to enrolment, included fewer patients with CM, and included more patients with previous experience with tafamidis or diflunisal. The impact of these differences on the results remains unknown, although subgroup analyses for these variables were generally consistent with the primary results. The NEURO-TTRansform study met its co-primary and key secondary end points at the interim analysis; therefore, further statistical testing was not conducted on these end points at the final analysis. Results at the final analysis were consistent with the interim analysis across all study end points, despite the switch from analysis of covariance (ANCOVA) at the interim analysis to a mixed model for repeated measures (MMRM) at the final analysis for end points of change from baseline in mNIS+7 score and change from baseline in Norfolk QoL-DN score. Given the use of the external placebo control, the MMRM for each end point 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 I or stage II 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 end point 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. Although it is 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 end point 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 modified Toronto Clinical Neuropathy Score [mTCNS]) are more frequently used, given their simplicity, although their use is not standardized across Canada. COMPASS-31 and R-ODS were exploratory outcomes of the NEURO-TTRansform study, although it did not include a comparison to placebo and should only be considered supportive, while the ONLS and 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 the 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 the NEURO-TTR study, the certainty of evidence started at low, acknowledging the nonrandomized 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 versus 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 nonrandomized study)	NA	9.23	0.22 (−3.46 to 3.90)	−9.01 (−13.48 to −4.54)	Low[b,c,d]	Eplontersen may result in lesser neurologic 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 nonrandomized study)	NA	25.06	0.30 (−4.46 to 5.06)	−24.76 (−30.96 to −18.56)	Low[b,d]	Eplontersen may result in lesser neurologic 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		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		NA	Very low[a,e]	The evidence is uncertain about the effect of eplontersen on R-ODS scores when compared with any comparator.

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		
Health-related quality of life							
Norfolk QoL-DN total score (−4 [best] to 136 [worst]), LSM change from baseline Follow-up: week 35	191 (1 nonrandomized study)	NA	8.67	−3.12 (−7.19 to 0.96)	−11.79 (−16.82 to −6.76)	Low[b,c,f]	Eplontersen may result in better HRQoL based on the change from baseline in 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 nonrandomized study)	NA	14.24	−5.50 (−10.03 to −0.96)	−19.74 (−25.63 to −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 nonrandomized study)	NA	−14.76	−81.20 (−84.55 to −77.84)	−66.43 (−71.39 to −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 nonrandomized study)	NA	−11.24	−81.65 (−84.82 to −78.48)	−70.42 (−75.17 to −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 nonrandomized 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 nonrandomized 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; hATTR = hereditary transthyretin amyloidosis; LSM = least squares mean; NA = not applicable; NR = not reported; PN = polyneuropathy; QoL-DN = Quality of Life – Diabetic Neuropathy; RCT = randomized controlled trial; R-ODS = Rasch-Built Overall Disability Score; SD = standard deviation.

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 (the NEURO-TTR study) 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 nonrandomized 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 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 MAIC and simulated treatment comparison (STC) comparing eplontersen from the NEURO-TTRansform study to inotersen from the NEURO-TTR trial, patisiran from 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 a statistically significant improvement in mNIS+7 composite score compared to inotersen [redacted]

For the change from baseline in Norfolk QoL-DN score, 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]

[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] Per cent 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 sponsor's feasibility assessment. Given the heterogeneity observed, the lack of a common comparator across the included trials, and the unique design of 2 studies that included randomized reference arms (the 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 diflunisal, proportion of patients with stage I and stage II disease, and 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 effective sample size (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 health care access and treatment approaches that are unrelated to V30M.

Two versions of the mNIS+7 were used in the analyses ($mNIS+7_{Ionis}$ and $mNIS+7_{Alnylam}$ composite scores). The $mNIS+7_{Ionis}$ composite score from the 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 time points 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 score, 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, although 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 hATTR-PN
Treatment	Eplontersen
Dose regimen	45 mg, once per month
Submitted price	$47,680.33 per prefilled single-dose pen
Submitted treatment cost	$572,164 per patient per year
Comparators	• Inotersen • Patisiran • Vutrisiran
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs

Component	Description
Time horizon	Lifetime (47 years)
Key data source	Efficacy of eplontersen informed by the NEURO-TTRansform study; efficacy of comparators informed by unanchored 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 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 CDA-AMC. • The sponsor's model lacked transparency, which prevented us 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 AEs on the cost-effectiveness of eplontersen was based on naive 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%.
Reanalysis results	• We were unable to address uncertainty in the comparative clinical evidence or identified limitations in the submitted economic evaluation. A 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 least expensive treatment used to treat hATTR-PN that is funded.

AE = adverse event; CDA-AMC = Canada's Drug Agency; DN = diabetic neuropathy; hATTR = hereditary transthyretin amyloidosis; ICER = incremental cost-effectiveness ratio; LY = life-year; PN = polyneuropathy; QALY = quality-adjusted life-year; QoL = quality of life; SAE = serious adverse event.

Budget Impact

We 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. In the absence of more reliable estimates to inform the parameters of the budget impact analysis, 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: Two expert committee members did not attend.

Conflicts of interest: None

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Questions or requests for information about this report can be directed to Requests@CDA-AMC.ca.