CADTH REIMBURSEMENT REVIEW

Patient and Clinician Group Input

eplontersen (TBC)

(AstraZeneca Canada Inc.)

Indication: Polyneuropathy in hereditary transthyretin-mediated amyloidosis.

April 22, 2024

This document compiles the input submitted by patient groups and clinician groups for the file under review. The information is used by CADTH in all phases of the review, including the appraisal of evidence and interpretation of the results. The input submitted for each review is also included in the briefing materials that are sent to expert committee members prior to committee meetings.

Patient Group Input

Transthyretin Amyloidosis Canada (TAC), previously known as Hereditary Amyloidosis Canada (HAC)

Name of Drug: *Eplontersen*
Indication: Used for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults
Name of Patient Group: Transthyretin Amyloidosis Canada (TAC), previously known as Hereditary Amyloidosis Canada (HAC)

Author of Submission: Anne Marie Carr, President and Founder, Transthyretin Amyloidosis Canada

About Transthyretin Amyloidosis Canada (TAC)

TAC is a not-for-profit organization that was established in 2019 to support individuals living with all forms of transthyretin amyloidosis, including hereditary (hATTR) and wild-type (wt-ATTR) amyloidosis, through community support, research, and education. TAC was inspired by the journey of our founder, Anne Marie Carr, who is living with hATTR amyloidosis. At the time of her diagnosis, Anne Marie realized the lack of community, support groups, information and resources available to her and her family, and thus began TAC.

Website – www.madhattr.ca

Information Gathering

Between November 2023 and February 2024, TAC engaged with Canadian patients and caregivers from both a qualitative and quantitative information gathering perspective. From a quantitative standpoint, TAC issued a 23-question online survey which was completed by 30 patients and caregivers from different provinces, including Ontario, Quebec, British Columbia, Alberta, Manitoba and Nova Scotia. From a quantitative perspective, TAC held 12 individual interviews with patients, based off a 25-question questionnaire. Each interview lasted between 45 to 60 minutes in length and the respondents were asked questions pertaining to their pre-diagnosis odyssey, duration of illness, hereditary and family history and experience with different therapies. Additionally, on February 13, 2024, TAC held a 2-hour roundtable discussion with patients and caregivers from across Canada. The main topics of discussion during the roundtable included health literacy of therapies for hATTR, shared-decision making / patient choice and tools, resources and support for patients and caregivers living with hATTR. In total, 51 patients and caregivers provided their input in either a qualitative or quantitative fashion. Because of the nature of transthyretin amyloidosis and the typical profile of patients diagnosed with the illness, all respondents were over the age of 65, with a near-even split between male (n=23) and female (n=28) patients.

Disease Experience

As the founder of TAC, I created this organization as a means to assist Canadians patients like myself who had no support or information upon diagnosis. My journey and experience in living with transthyretin amyloidosis is, unfortunately, not anomalous, but instead a pattern of doctor's visits, tests, hardship, pain, suffering and frustration.

I first noticed neuropathy symptoms and initially dismissed them, attributing them to time spent at my keyboard or simply carpal tunnel syndrome. I developed cardiac symptoms within a few years of noticing my neuropathy.

These symptoms eventually developed into heart failure, including tightness, palpitations, lightheadedness, shortness of breath, low energy, trouble sleeping, tiredness, low blood pressure, autonomic dysfunction, fluid retention and feelings of being full all the time despite not having eaten much. I have a heart murmur, and my echocardiograms sometimes vary drastically. My ejection fraction can vary from 20%-33%. My cardiac walls are often thicker.

I have trouble eating, often choke on food, my liver is distended, and I experience gastrointestinal symptoms, particularly diarrhea. At times, I have lost control of my bowels.

One leg often trails behind the other when climbing stairs, so I fall often.

I had a cardiac arrest in 2017, and had a dual pacemaker and defibrillator implanted.

As ATTR is a progressive illness, my symptoms are progressing and will not ever return to normal. In addition to the symptoms listed above, I have difficulty sleeping and am often fatigued during the day. I have also noticed my energy is decreasing over time and I am not able to do the things I was able to do even a few years ago. I struggle to walk, have numbness & foot pain, which makes it extremely difficult to navigate stairs or even regular walking. When I do attempt any walking, it requires rest often and for an extended period.

Due to my ATTR, I do not visit easily with friends or family outside of our home - it takes a significant amount of time to get ready and thoughtful planning. I will not have my granddaughter visit when I am home alone.

My neuropathy is also getting worse; I have increasing difficulty with fine motor skills. I constantly drop things and struggle to pick them up. I get severe cramps from my elbows to my wrists, and my fingers often lock. I struggle to write or type. One of my legs often trails behind the other, this results in balance issues causing me to fall.

Overall, there is not a single aspect of my life – physical or emotional – that has not been affected by amyloidosis. As mentioned previously, this is unfortunately the norm for many patients, especially those who are inadequately treated.

Experiences With Currently Available Treatments

There are currently three treatments available to different forms of transthyretin amyloidosis. These treatments include:

TAFAMIDIS, VYNDAQEL
Tafamidis is used in the treatment of adult patients, with cardiomyopathy due to transthyretin-mediated amyloidosis, wild-type or hereditary, to reduce cardiovascular mortality and cardiovascular-related hospitalization.

TEGSEDI
Hereditary Amyloidosis Transthyretin (hATTR) is an under-recognized, debilitating and progressive disease that is caused by the buildup of Transthyretin proteins that misfold due to inherited mutations. It is characterized by the deposition of amyloid fibrils throughout the body including in nervous tissue and can have a devastating impact on patients' quality of life. TEGSEDI is a once-weekly, at-home subcutaneous injection that targets the polyneuropathy of hATTR amyloidosis at its source by reducing production of the Transthyretin protein.

ONPATTRO
ONPATTRO is a prescription medicine that treats the polyneuropathy caused by hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis). ONPATTRO is used by adults only.
It is characterized by the deposition of amyloid fibrils throughout the body including in nervous tissue and can have a devastating impact on patients' quality of life. ONPATTRO is administered once every 3 weeks by an infusion c that targets the polyneuropathy of hATTR amyloidosis at its source by reducing production of the Transthyretin protein.

All three therapies are approved by Health Canada and have varying degrees of public reimbursement in different provinces. All three therapies have their benefits and also their side effects. For example, I need to go to the hospital for infusions of Onpattro, which is challenging. Though my nurses are friendly, and I like them, it is time-consuming going to the hospital regularly. The hospital is 1.5 hours away, so that makes it a 3-hour round trip, not including the time spent infusing my therapy. It can be expensive for patients, having to pay for travel, parking, and potentially take time away from work and other activities.

The costs of medications are also prohibitive, and I could never pay for these personally. I am no longer able to work due to this illness, which makes the additional costs of treatment even that much harder to bear.

Improved Outcomes

Currently available therapies to treat hATTR are great and may be preferred and in fact needed by some. However, given the age of patients affected by hATTR, along with the already significant dependency challenges brought about by the disease, eplontersen does have some unique advantages that can lead to meaningfully improved outcomes for some patients. These advantages may include:

- Mode of Administration and Convenience - According to patients and caregivers surveyed in TAC's qualitative analysis, 83.3% of respondents (25/30) felt travelling for medical appointments and/or treatment infusions was highly or somewhat invasive. Additionally, 80.0% of respondents (24/30) felt home administration was an important attribute for a therapy.

  As the first and only therapy that can be self-administered at home via an auto-injector, eplontersen may be a far more convenient option than previous therapies. This means patients are able to learn and self-administer their therapy, allowing for far more freedom and less reliance on infusion networks and clinic visits. It is important to note, clinic visits are not an individual endeavour, but a dual-effort including a patient's caregiver. Missing a day of work to travel to an infusion centre is also eliminated through self-administration. This self-administration also eliminates the necessity of pre-medicine prior to therapy. This mode of administration and consequent autonomy may allow patients the ability to live their lives as normally as possible, without the disturbances of constant dosing and clinic visits.
- Quality of Life – In a multi-system disease such as hATTR, autonomy goes beyond the necessity to attend clinical and infusion appointments. According to the 2-hour roundtable and qualitative interviews, loss of autonomy is one of the single greatest quality of life losses felt by patients and caregivers alike. This loss of autonomy permeates through every activity and has an immeasurable impact on many facets of a patient's life including:
    - Ability to maintain a career – 66.7% of respondents (20/30) from the patient survey have had to either stop working, retire early or scale back to less than 15 hours per week due to hATTR;
    - Travel – 80% of respondents (24/30) feel hATTR has a significant or somewhat significant impact on their ability to travel

    - Social life – in all qualitative interviews, patients feel hATTR has had a significant impact on their ability to maintain a social life. Patients relayed that their psyche and whole identity is engrossed in hATTR and this is partially due to the need to constantly be planning their whole lives around medical and infusion appointments.

- Treatment Options – It is well-documented that not every therapy works equally as well in every patient. As such, allowing patients and physicians access to different treatment options, particularly in a rare-multi-system disease such as hATTR, is paramount in ensuring no patient is left behind. Given that eplontersen is the only approved therapy that can be self-administered via auto-injector further adds to its importance as a unique treatment option of patients.
- Hospital admissions may be decreased with patients on correct therapy, which decreases the pharmacoeconomic burden of illness related to TTR-amyloidosis. At a time where hospitals remain over-burdened due to the pandemic, keeping patients who are typically elderly and already have frail immune systems, away from hospital centres is a key impetus for maintaining optimal health.

Experience With Drug Under Review

Due to privacy laws protecting patients' identities in Canada, we were unable to obtain any patient input directly from Canadians who participated in the eplontersen clinical trials. However, all respondents from the qualitative interviews, as well as feedback obtained during the 2-hour roundtable meeting, spoke to the void eplontersen can satiate as the only therapy that can be self-administered via auto-injector.

It is important to remember that hATTR is a disease highly characterized by its psychological impact on patients, in addition to the vast physical co-morbidities. This psychological impact is primarily associated with a lack of autonomy and a total loss of independence. A therapy that has the ability to remove the shackles of dependence on infusion centres, can be conveniently stowed and carried with a patient anywhere they go and can be administered simply and easily goes a long way in helping return a measure of control in their lives.

Overall, there are many ways in which the symptoms and co-morbidities of ATTR can impact a patient's life. Current therapeutic intervention is extremely important in limiting the symptoms, progression and co-morbidities of ATTR, but are also often associated with inconveniences that patients suffer through in order to experience the therapeutic benefits. With eplontersen, patients can attain the therapeutic benefit without the limiting inconveniences.

Anything Else?

Transthyretin amyloidosis is a disease characterized by high phenotype variability, primarily due to the fact that amyloid deposits can be found in almost every part of the body. This, of course, leads to expressivity that is different in almost every patient; patients can demonstrate an infinite combination of symptoms including neurological, cardiac, gastrointestinal, ophthalmologic, fatigue, urologic, muscular, and so on. In the quantitative patient questionnaire, patients identified 18 different symptoms they experience on a regular basis, which is consistent with a multi-system disease like ATTR. As such, due to this phenotype variability and expressivity, it is paramount to have as many therapies approved and accessible for patients, in order to ensure no patient is left without appropriate treatment.

Conflict of Interest Declaration - Transthyretin Amyloidosis Canada (TAC)

To maintain the objectivity and credibility of the CADTH reimbursement review process, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This Patient Group Conflict of Interest Declaration is required for participation. Declarations made do not negate or preclude the use of the patient group input. CADTH may contact your group with further questions, as needed.

Did you receive help from outside your patient group to complete this submission?

No.

Did you receive help from outside your patient group to collect or analyze data used in this submission?

No.

Table 1: Financial Disclosures for Transthyretin Amyloidosis Canada (TAC)

Check Appropriate Dollar Range With an X. Add additional rows if necessary.

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Alnylam	-	-	-	X
SOBI	-	-	X	-
Pfizer	-	-	-	X
Intellia	-	X	-	-
Astra Zeneca	-	-	X	-
Bridge Bio	-	-	X	-

I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

Name: Anne Marie Carr
Position: Founder & Executive Officer
Patient Group: Hereditary Amyloidosis Canada
Date: April 15 2024

Clinician Group Input

Neuromuscular Disease Network for Canada

CADTH Project Number: SR0826-000

Generic Drug Name (Brand Name): eplontersen

Indication: Hereditary transthyretin amyloidosis polyneuropathy (hATTR-PN)

Name of Clinician Group: Neuromuscular Disease Network for Canada Author of Submission: Vera Bril, MD, FRCPC; and

Genevieve Matte, MD, FRCPC

Hanns Lochmuller, MD, FRCPC
Michelle Mezei, MD, FRCPC

Nowell Fine, MD, FRCPC Hans Katzberg, MD, FRCPC Dubravka Dodig, MD, FRCPC

About Your Clinician Group

The Neuromuscular Disease Network for Canada (NMD4C) is the new 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.

Launched in January 2020 with funding from the Canadian Institutes of Health Research (CIHR) and Muscular Dystrophy Canada (MDC), NMD4C builds on existing national initiatives such as the Canadian Neuromuscular Disease Registry (CNDR), the Canadian Pediatric Neuromuscular Group (CPNG), and the former neuromuscular network CAN-NMD. Themission of NMD4C is to improve the care, research and treatment of NMDs for all Canadians. Its vision is to be a comprehensive, inclusive, open and enduring network through which Canadian stakeholders can share expertise and data and collaborate on joint activities and research for the benefit of Canadian patients.

The network's goals are to:

- Formalize and sustain a network of NMD stakeholders united around a cohesive three-year work plan
- Train and educate the next generation of NMD stakeholders (clinicians, scientists, and patient advocates)
- Raise the standard of care for NMD and access to therapies across Canada
- Strengthen biomedical and clinical infrastructure to build research capacity in Canada

As NMD4C members and neuromuscular clinicians across Canada with significant clinical expertise in the management of patients with hereditary transthyretin amyloidosis polyneuropathy, we are writing to offer our strong support for favorable benefit access for eplontersen as a treatment option in Canada.

Information Gathering

Please describe how you gathered the information included in the submission.

Clinicians with experience treating hereditary transthyretin amyloidosis polyneuropathy (hATTR-PN) polyneuropathy, including those with experience with novel biologics, and those who were part of the published Canadian guidelines for hATTR-PN were asked to contribute to this submission. These expert clinicians contribute to the knowledge of hATTR-PN and its treatments and are involved in clinical and observational research, clinical guidelines development and health technology assessment. The clinicians contributing herein are familiar with the data from clinical trials on treatments for hATTR-PN, including eplontersen.

Current Treatments and Treatment Goals

Please describe the current treatment paradigm for the disease.

- Focus on the Canadian context.
- Please include drug and non-drug treatments.
- Drugs without Health Canada approval for use in the management of the indication of interest may be relevant if they are routinely used in Canadian clinical practice. Treatments available through special access programs are relevant. Are such treatments supported by clinical practice guidelines?
- Do current treatments modify the underlying disease mechanism? Target symptoms?
- What are the most important goals that an ideal treatment would address?
- **Examples:** Prolong life, delay disease progression, improve lung function, prevent the need for organ transplant, prevent infection or transmission of disease, reduce loss of cognition, reduce the severity of symptoms, minimize adverse effects, improve health-related quality of life, increase the ability to maintain employment, maintain independence, reduce burden on caregivers.

hATTR-PN is staged as: Stage 1 PN present and the patient is able to ambulate without assistance; Stage 2 PN includes motor weakness and the need for ambulatory aids; and Stage 3 the presence of generalized weakness, cachexia and incontinence with the inability to ambulate (wheel-chair or bedridden). The progression of hATTR-PN from diagnosis to death across these stages is a median of 4.7 years, death occurring due to cachexia, cardiac insufficiency and infections.

The treatment landscape for hATTR-PN includes multiple interventions: supportive care, symptom alleviation and disease-modifying approaches as well as referral for multidisciplinary care, particularly cardiology. Canadian

guidelines for the diagnosis, monitoring and treatment of hATTR-PN have been published (Alcantara M, Mezei MM, Baker SK, Breiner A, Dhawan P, Fiander A, Fine NM, Hahn C, Katzberg HD, Khayambashi S, Massie R, Matte G, Putko B, Siddiqi Z, Delgado D, Bril V. Canadian Guidelines for Hereditary Transthyretin Amyloidosis Polyneuropathy Management. Can J Neurol Sci. 2022 Jan;49(1):7-18. doi: 10.1017/cjn.2021.34. Epub 2021 Feb 26. PMID: 33631091.) These guidelines include recommendations for the use of novel TTR gene silencing therapies (inotersen [antisense oligonucleotide] and patisiran [RNA interference], as those were available at the time of publication). These drugs more reliably halt disease progression compared to older medications, diflunisal (nonsteroidal anti- inflammatory drug) and tafamidis (protein stabilizer). Continued PN progression and decline was observed in over 75% of patients treated with protein stabilizers. Diflunisal is not available in Canada and tafamidis was not approved for PN by Health Canada due to lack of sufficient efficacy data.

In Canada, The CADTH initially recommended inotersen and patisiran to be reimbursed for polyneuropathy treatment in adult patients and recognized that both showed a statistically significant improvement for the primary and secondary endpoints of the pivotal studies (APPOLO and NEURO-TTR). The report for patisiran included an indirect treatment comparison submitted by the manufacturer, and the analyses suggested that patisiran was statistically superior to inotersen for the change from baseline in the mNIS and in the Norfolk QoL-DN scores. After the approval of those two orphan drugs in 2019, patisiran has been the most commonly used therapy in patients with hATTR-PN, as some patients who were initially treated with inotersen were discontinued due to side-effects.

In February 2024, the CADTH Canadian Drug Expert Committee (CDEC) recommended that vutrisiran, the newest double-stranded small interfering ribonucleic acid (siRNA), be reimbursed for the treatment of stage 1 or stage 2 polyneuropathy in adult patients with hATTR amyloidosis, genetically confirmed, with no severe heart failure (NYHA class III or IV) and no previous liver transplant. Like patisiran, this medication can reduce vitamin A levels, therefore supplementation is advised, sometimes with higher doses than the recommended daily allowance, as serum vitamin A levels do not reflect the total vitamin in the body. The recommended dosage of vutrisiran is 25 mg, to be administered by subcutaneous injection by a health professional once every 3 months. CDEC also acknowledged that among currently available treatments, patisiran is the most commonly used therapy but with the inconvenience of being administered by IV infusion every 3 weeks.

Another discussion point by CDEC noted that robust data comparing patisiran and inotersen, the treatment options available at that time, was lacking and the choice between those therapies was guided by availability, route and frequency of administration, patient preference, and contraindications. The novel agent, vutrisiran, had the potential to be used in patients with cardiac manifestations related to amyloidosis, which could offer an advantage

to transition those patients to this therapy. Regarding safety profile, it was anticipated that vutrisiran would be similar to patisiran, however uncertainty regarding adverse effects exists, given the absence of long-term safety data and the relatively small sample sizes in previous studies.

The overarching goals of hATTR-PN therapy are to prevent morbidity and reduce mortality, minimize hospital visits, and enhance the quality of life. Given that hATTR-PN is an autosomal dominant disorder, managing families with the ATTR gene is of paramount importance to ensure early diagnoses and treatment to avoid irreversible nerve damage with consequent early disability and death. Caregiver burden is also a consideration when choosing the most appropriate therapy. Additional considerations about drug effectiveness, patient independence, convenience and side-effect profile are also important dimensions that have to be analyzed before choosing the most appropriate therapy.

Treatment Gaps (unmet needs)

1.1. Considering the treatment goals in Section 3, please describe goals (needs) that are not being met by currently available treatments.

More than 75% of patients on protein stabilizers show disease progression and therefore these therapies are sub-optimal and not available for hATTR-PN in Canada. Inotersen therapy is associated with thrombocytopenia and renal toxicity. As a result, patients elected to transition to the alternate, patisiran, although the required every 3 week intravenous infusions place a burden on the patient.

The novel product eplontersen (ION-682884) is a follow-on compound of inotersen that incorporates Ligand-Conjugated Antisense (LICA) technology and targets the asialoglycoprotein receptors (ASGPR) that are expressed abundantly on hepatocytes. In comparison to inotersen, eplontersen requires a lower dose and frequency of administration to achieve a similar reduction in ATTR. While inotersen is given subcutaneously every week, eplontersen is given subcutaneously every 4 weeks, resulting in more convenience for the patient and potentially in more compliance.

Inotersen will no longer be available to patients in the US starting on 9/27/24 and the status in Canada of inotersen is uncertain; therefore when, and if as is likely, this medication also becomes unavailable in Canada, there will be only two options of disease modifying agents: patisiran and vutrisiran, with apparently similar clinical and safety profiles. Eplontersen will offer additional choice for patients and potentially a difference in outcomes in comparison with the above-mentioned drugs and could be a suitable treatment option for selected patients. An ongoing Phase 3 global,

double-blind, randomized, placebo-controlled study aims to assess the efficacy and safety of eplontersen in hATTR-CM or wtATTR-CM in patients already receiving standard of care therapy. The dosing scheme is also once every 4 weeks, which, if positive, could be a good option to target patients with multiple manifestations of the disease. Currently, hATTR-CM patients receive tafamidis and if hATTR-PN becomes evident, then the patients are switched to patisiran or vutisiran. Additional therapeutic options are beneficial to patients for choice and also in case they fail to respond to one option, others exist for their treatment.

Place in Therapy

1.2. How would the drug under review fit into the current treatment paradigm?

Mechanism of Action and Complementarity

Antisense oligonucleotides (ASO) such as inotersen and eplontersen and small interfering RNA (siRNA) such as patisiran and vutrisiran are all molecules capable of silencing gene expression. Both ASO and siRNA-based strategies utilize a complementary oligonucleotide, however the mechanism of action differs between ASOs and siRNA. Gene silencing using an ASO works with a single-stranded oligonucleotide that directly binds to its target RNA after being delivered into cells or dosed in vivo, a technology that has been successfully developed for other orphan diseases. For instance, ASO therapies have been approved for other neuromuscular disorders such as nusinersen for spinal muscular atrophy and eteplirsen for Duchene muscular dystrophy *(approved in the US only*). However, it is unknown whether failure to respond to one agent indicates that failure to a different agent would occur. So, the option to change drugs provides extra scope for the patient to respond to treatment. Although liver transplantation has been eliminated in most patients due to these novel drugs, there are cases where progression still occurs (as it does after liver transplantation) and these patients are sometimes offered liver transplant as a final therapeutic option despite having been treated with gene silencers (usually 2 in sequence).

Addressing the Underlying Disease Process

RNA silencers and gene editing tools target the TTR mRNA or gene, aiming to reduce serum TTR levels. Both ASOs and siRNAs were designed to alter the disease process by degrading both wild-type and variant TTR transcripts, with a final aim to reduce the synthesis of TTR protein.

Placement in the Treatment Paradigm

Although eplontersen is not the first agent to be approved, it seems to have advantages over inotersen, not only regarding side effects but also in effectiveness. Eplontersen is a high-affinity ligand, that facilitates uptake by a tissue-specific receptor in the hepatocytes. In the phase 1 trial done in healthy volunteers, eplontersen showed a 30-

fold increase in potency in reducing TTR levels compared to inotersen. This difference in potency supports patients having the availability of eplontersen.

Suitability for Specific Patient Populations

Given the results of Phase 3 clinical trials and others that are currently underway, eplontersen may be useful to halt or reduce disease progression in patients with ATTRv-PN and all types of ATTR-CM, which has an advantage over the currently available therapies. Furthermore, no severe or serious adverse events, and no significant abnormalities in renal or hematological function were reported.

Expected Shift in Treatment Paradigm

The main advantages are less frequent dosing by these new hepatic targeted drugs, which may improve patient burden and compliance. Additionally, the conjugated ASOs (such as eplontersen) have improved efficacy and safety profiles. In the near future, gene editing tools could potentially require a single dose, which would be an excellent addition to the currently available treatments.

Recommendation on Treatment Initiation

As TTR-mediated amyloidosis is a progressive disease with various serious clinical manifestations new technologies targeting the hepatocytes, the primary location of TTR synthesis, should be initiated as soon as the patient is diagnosed. Given that the clinical manifestations occur after significant build-up of amyloid has occurred in the body, the earlier the therapies are initiated the better the outcomes.

1.3. Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

Which patients are most likely to respond to treatment with drug under review?

Patients in the initial phases of the disease (stage 1 PN) or who have not progressed significantly (stage 2 PN) are most likely to respond to the drug.

Which patients are most in need of an intervention?

Patients who present with several different disease manifestations including mainly polyneuropathy and cardiomyopathy are most in need of an intervention given the significant morbidity and mortality and reduced quality of life.

Would this differ based on any disease characteristics (e.g., presence or absence of certain symptoms, stage of disease)?

The expectation is that patients who present with both polyneuropathy and cardiomyopathy can be responsive to therapy, and stage of disease is certainly a characteristic that will impact response to treatment.

How would patients best suited for treatment with drug under review be identified (e.g., clinician examination/judgement, laboratory tests (specify), diagnostic tools (specify))

Patients can be identified by clinician judgement, by training and awareness of the medical community. Collaborations between the general practitioner and specialists (cardiologists, neurologists) would be very helpful in this regard. We believe that increasing awareness in communities that may have a higher prevalence of the disease and different ages of presentation (such as the Portuguese community) would help diagnose patients in earlier stages. Currently, diagnosis is based on the neurological history and examination and nerve conduction studies followed by genetic testing. Tests of small nerve fibre function, where available, should complement the standard methods of diagnosing patients. Several patterns of hATTR-PN presentation are common, but not exclusive. They include: autonomic neuropathy, small fibre polyneuropathy, length-dependent sensorimotor polyneuropathy, early carpal tunnel syndrome.

Are there any issues related to diagnosis?

Family counseling is one of the main issues of diagnosing any hereditary, progressive disease. Clinics with multidisciplinary teams would be very helpful in providing the highly specialized level of care those patients require. Demystifying the consequences of the genetic tests and focusing on the benefits of early diagnosis are strategies that can help minimize the impact of such diagnosis.

Another area of concern is that, excepting the genetic testing, the presentation of polyneuropathy in hATTR-PN can mimic other polyneuropathies, raising the need for neuromuscular expertise in the diagnosis, monitoring and treatment of hATTR-PN patients.

Is a companion diagnostic test required?

Patients with amyloidosis require an extensive diagnostic protocol that includes an assessment by a neurologist, electrodiagnostic tests (nerve conduction studies) and cardiac assessment.

Is it likely that misdiagnosis occurs in clinical practice (e.g., underdiagnosis)?

Given that amyloidosis is a rare disease, data from recent publications suggest that both peripheral nerve and cardiac amyloidosis are underdiagnosed diseases. The improvement of diagnostic techniques (including imaging in cardiac amyloidosis) has made it possible to recognize common phenotypes (that are thought to be caused by other diseases), such as patients with hypertensive heart disease, hypertrophic cardiomyopathy, or heart failure with preserved systolic function and neuropathies previously labeled as idiopathic. Misdiagnoses occur when the

neuropathy mimics other treatable forms of neuropathy, for example CIDP, leading to expensive and ineffective treatments being offered.

Is it possible to identify those patients who are most likely to exhibit a response to treatment with drug under review?

We believe that patients in the early stages of disease will respond better. They can be identified by a thorough examination by a neurologist, along with electrodiagnostic tests, that will help grade the disease stage/progression. Furthermore, cardiac assessments may also help stratify patients with a better prognosis for certain interventions. However, beyond stage of disease at diagnosis for hATTR-PN, there is no proven test to identify patients who will respond to treatment.

5.3 What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

Are outcomes used in clinical practice aligned with the outcomes typically used in clinical trials?

Outcomes in clinical trials need to be robust and sensitive to change, and are often not feasible in clinical practice. Some outcomes used in recent trials of amyloidosis involve extensive testing with devices that are not readily available in clinical practice.

Furthermore, they require extensive training. The NIS-7 involves testing for more than ½ day, also not practical for clinical practice. That is why the recommendations in the Canadian guidelines are to use the neurological history and examination and nerve conduction studies, and not the NIS-7 when monitoring patients with hATTR-PN.

What would be considered a clinically meaningful response to treatment? Consider the magnitude of the response to treatment. Is this likely to vary across physicians?

The meaningful responses may vary across physicians, therefore training and homogeneity in outcome measures, along with serial follow-ups can be helpful in this scenario. A clinically meaningful response would be stability or slower progression of the symptoms and functional abilities and improved survival as compared to the natural history of the disease. In clinical practice, outcomes such as loss of walking ability and deterioration of cardiac measures despite intensive treatment could help identify those who are not responding to treatment. In this context, staging of hATTR-PN is useful. Nerve conduction studies are also objective measures of nerve function and structure and complement the clinical evaluations. Another useful measure is the Norfolk quality of life outcome which can be administered more easily in clinic and help monitor patients' overall well-being related to their polyneuropathy.

5.4 What factors should be considered when deciding to discontinue treatment with the drug under review?

We believe that there is still a long way to go with the understanding of all the effects (including side-effects) of the new hepatically- targeted treatments. Its effects on certain ATTR phenotypes such as neuropathy have to be closely monitored with serial neurologic and cardiologic assessments. When a significant progression has occurred, such as the patient transitioning from walking with aids to a wheelchair, it is very likely that the medications are not proving effective. Furthermore, the potential for amyloidosis involving the CNS and ocular amyloidosis will likely grow as more patients receive RNA silencers that prolong life and delay disability. It should be kept in mind that even with liver transplant, progression of hATTR-PN occurs, so there is no simple answer.

5.5 What settings are appropriate for treatment with [drug under review]? Is a specialist required to diagnose, treat, and monitor patients who might receive [drug under review]?

Appropriate Settings for Treatment

1. Specialty Clinic: The most appropriate settings for identification and treatment of those patients are tertiary centers, with specialized and multidisciplinary approaches including neuromuscular experts and lines of referral to cardiologists and other specialists for this multidisciplinary disorder.
2. Hospital Outpatient Clinic: Neuromuscular clinics and specialized cardiology clinics.
3. Community Setting: Neurological clinics with referral lines to neuromuscular expertise.

Requirement for a Specialist

The diagnosis, initiation of treatment, and ongoing management of patients on eplontersen ideally require the involvement of specialists due to the complexity of the disease and the specialized nature of this treatment. Relevant specialties include:

- Neurology
- Neuromuscular Specialists
- Cardiologists
- GI specialists, as required Ophthalmologists, as required.

- Nephrologists, as required.

- Nurse specialized in neurology/neuromuscular settings
- Occupational therapist
-Physical and Rehabilitation Medicine (Physiatry) , as required
-Medical Genetics

Additional Information

Is there any additional information you feel is pertinent to this review?

The more therapeutic options available for patients, the better since there is no guarantee of response to limited therapies.

Conflict of Interest Declarations

To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This conflict of interest declaration is required for participation.

Declarations made do not negate or preclude the use of the clinician group input. CADTH may contact your group with further questions, as needed. Please see the *Procedures for CADTH Drug Reimbursement Reviews* (section 6.3) for further details.

Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.

No

Did you receive help from outside your clinician group to collect or analyze any information used in this submission? If yes, please detail the help and who provided it.

No

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review. **Please note that this is required for each clinician who contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.**

1.2 Declaration for Clinician 2

Name: Genevieve Matte

Position: Neurologist, CHUM

Date: 18 March 2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

1.2.1 Table 2: Conflict of Interest Declaration for Clinician 2

Company	Check appropriate dollar range*			
	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
Astra-Zeneca		x		
Alnylam			x	
Sobi	x			
Akcea		x		

* Place an X in the appropriate dollar range cells for each company.

1.3 Declaration for Clinician 3

Name: Hanns Lochmuller

Position: Neurologist, Senior Scientist

Professor of Neurology, University of Ottawa Faculty of Medicine and The Ottawa Hospital Department of Medicine Date: 19-03-2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation. *None to disclose.*

1.3.1 Table 3: Conflict of Interest Declaration for Clinician 3

Company	Check appropriate dollar range*			
	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
Add company name				

Add company name				
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

1.4 Declaration for Clinician 4

Name: Michelle Mezei

Position: Clinical Professor, Division of Neurology, University of British Columbia Date:

19-03-2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

1.4.1 Table 4: Conflict of Interest Declaration for Clinician 4

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Alnylam				X
Sobi/Akcea		X		
AstraZeneca		X		
Ionis	X			

* Place an X in the appropriate dollar range cells for each company.

1.5 Declaration for Clinician 5

Name: Nowell Fine

Position: Cardiologist, Associate Professor Date:

22-03-2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

1.5.1 Table 5: Conflict of Interest Declaration for Clinician 5

	Check appropriate dollar range*

Company	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
Pfizer	X			
AstraZeneca	X			
Alnylam	X			
NovoNordisk	X			

* Place an X in the appropriate dollar range cells for each company.

1.6 Declaration for Clinician 6

Name: Hans Katzberg

Position: Neurologist, Associate Professor of Neurology Date:

24-03-2024

1.6.1 Table 6: Conflict of Interest Declaration for Clinician 6

Company	Check appropriate dollar range*			
	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
CSL Behring			X	
Grifols	X			
Octapharma			X	
Takaeda			X	
Alexion			X	
UCB			X	
ArgenX			X	
Roche	X			
Dyne	X			
Abcuro		X		
Immunovant	X			
Dianthus		X		

* Place an X in the appropriate dollar range cells for each company.

1.7 Declaration for Clinician 7

Name: Dubravka Dodig

Position: Staff Neurologist at UHN/Toronto Western Hospital

Date: 02-04-2024

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

1.7.1 Table 7: Conflict of Interest Declaration for Clinician 7

* Place an X in the appropriate dollar range cells for each company.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Alexion AstraZeneca	☐	☐	☒	☐
Argenx	☐	☒	☐	☐