Canadian Journal of Health Technologies
February 2024 Volume 4 Issue 2

CADTH Reimbursement Recommendation

Vutrisiran (Amvuttra)

Indication: For the treatment of stage 1 or stage 2 polyneuropathy in adult patients with hereditary transthyretin-mediated amyloidosis
Sponsor: Alnylam Pharmaceuticals BV
Final recommendation: Reimburse with conditions

Summary

What Is the CADTH Reimbursement Recommendation for Amvuttra?

CADTH recommends that Amvuttra be reimbursed by public drug plans for the treatment of stage 1 or stage 2 polyneuropathy in adult patients with hereditary transthyretin-mediated (hATTR) amyloidosis if certain conditions are met.

Which Patients Are Eligible for Coverage?

Amvuttra should only be covered to treat adults with stage 1 or stage 2 genetically confirmed hATTR amyloidosis with polyneuropathy (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 Amvuttra should be assessed at least every 6 months to determine whether they would benefit from continued treatment. Treatment with Amvuttra 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?

Amvuttra 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 drugs or transthyretin stabilizers. The cost of Amvuttra should be reduced so that it does not cost more than other drugs for hATTR amyloidosis.

Why Did CADTH Make This Recommendation?

- Evidence from a clinical trial showed that, in patients with hATTR-PN, treatment with Amvuttra improved neuropathy-related neurologic function and quality of life, and reduced disability due to neuropathy, when compared to treatment with placebo. In addition, the trial's results suggested that Amvuttra had similar efficacy and safety as the currently available treatment option, patisiran.
- Amvuttra provides a subcutaneous drug option with less frequent administration that can be administered in a patient's home, which addresses a need identified by patients.
- Based on CADTH's assessment of the health economic evidence, Amvuttra does not represent good value to the health care system at the public list price. The committee determined that there is not enough

Summary

evidence to justify a greater cost for Amvuttra compared with the least costly treatment reimbursed for hATTR-PN.

- Based on public list prices, Amvuttra is estimated to cost the public drug plans approximately $23.8 million over the next 3 years.

Additional Information

What Is hATTR Amyloidosis?

hATTR amyloidosis is caused by alterations in a gene that makes a protein called TTR. As a result of this genetic alteration, an abnormal protein called amyloid builds 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 amyloidosis is considered a rare disease, affecting about 10,000 people worldwide.

Unmet Needs in hATTR Amyloidosis

Patients with hATTR-PN need effective treatments that slow disease progression, have a low risk of adverse events (AEs), provide a convenient route of administration, and have infrequent dosing.

How Much Does Amvuttra Cost?

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

Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that vutrisiran be reimbursed for the treatment of stage 1 or stage 2 polyneuropathy in adult patients with hATTR amyloidosis only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

Evidence from 1 phase III, multicentre, open-label trial (HELIOS-A) demonstrated that compared with an external placebo group (from the APOLLO trial), treatment with vutrisiran resulted in added clinical benefit in adults with stage 1 or stage 2 hATTR-PN compared to placebo. At 18 months, vutrisiran, compared with placebo, was associated with statistically significant and clinically meaningful improvements in neurologic function, as measured by the modified Neuropathy Impairment Score +7 (mNIS+7) (mean difference between groups = −28.6 points; 95% confidence interval [CI], −34.0 to −23.1), in health-related quality of life (HRQoL), as measured by the Norfolk Quality of Life–Diabetic Neuropathy Questionnaire (Norfolk QoL-DN) (mean difference between groups = −21.0 points; 95% CI, −27.1 to −14.9), and in disability, as measured by the Rasch-built Overall Disability Scale (R-ODS) (mean difference between groups = 8.4 points; 95% CI, 6.5 to 10.4). The polyneuropathy disability (PND) score, an exploratory outcome, was supportive of the benefits observed with vutrisiran compared with placebo.

CDEC assessed the available evidence of comparative efficacy of vutrisiran versus the current treatment option, patisiran. The HELIOS-A trial demonstrated statistically significant noninferiority (i.e., the noninferiority margin of 10% was met) in serum TTR level percent reduction through month 18 with vutrisiran compared with the within-study patisiran group (median difference between groups = 5.28%; 95% CI, 1.17% to 9.25%). These results were supported by a post hoc analysis of the HELIOS-A trial, suggesting that improvements in efficacy outcomes (i.e., mNIS+7, Norfolk QoL-DN score, and R-ODS score) with vutrisiran were similar to those observed with the within-study patisiran group. Although there were several limitations to a submitted indirect treatment comparison that compared vutrisiran with patisiran, the results in efficacy outcomes (i.e., PND score, mNIS+7, Norfolk QoL-DN score) did not suggest a trend of 1 drug being superior to the other.

Patients identified a need for treatments that provide a more convenient route of administration and less frequent dosing, and a lower risk of AEs, including falls. CDEC noted that vutrisiran met some of the needs identified by patients by providing a subcutaneous drug option with less frequent administration that can be administered in a patient's home; however, no evidence was available related to the impact of vutrisiran's more convenient administration on efficacy outcomes. CDEC noted that vutrisiran had a similar safety profile to patisiran and no new safety concerns were observed; however, uncertainty remained in the absence of long-term safety data and relatively small sample sizes.

At the sponsor-submitted price for vutrisiran and publicly listed price for all comparators, vutrisiran was more costly than the currently available treatments for hATTR-PN. As there is insufficient evidence to suggest that

vutrisiran is more effective than its comparators, the total drug cost of vutrisiran 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		
1. Treatment with vutrisiran should be reimbursed in adult patients with stage 1 or stage 2 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 HELIOS-A trial, vutrisiran demonstrated clinically meaningful benefits for patients with stage 1 or stage 2 hATTR-PN when compared to placebo. Patients with advanced polyneuropathy (i.e., PND stage IV or FAP stage III) and prior liver transplant were excluded from the HELIOS trial; therefore, there is no evidence to support the use of vutrisiran 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 vutrisiran.	According to the clinical expert, 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. In addition, it is common to monitor TTR levels in patients as part of monitoring response to treatment. Timing of assessments depends on the severity of the disease (if asymptomatic or minimally symptomatic, yearly assessments is acceptable); in patients with more active disease, assessments every 3 or 6 months are appropriate.	—
Discontinuation		
3. Treatment with vutrisiran 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 vutrisiran in patients whose disease has progressed is effective.	—

Reimbursement condition	Reason	Implementation guidance
Prescribing		
4. The patient must be under the care of a specialist with experience in the diagnosis and management of hATTR-PN.	This will help ensure that vutrisiran is prescribed only for appropriate patients and adverse effects are managed in an optimized and timely manner.	—
5. Vutrisiran should not be used in combination with other interfering ribonucleic acid drugs or transthyretin stabilizers used to treat hATTR.	There are no data supporting the efficacy and safety of vutrisiran when used in combination with other interfering ribonucleic acid drugs or transthyretin stabilizers.	—
Pricing		
6. Vutrisiran 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 vutrisiran over the least costly treatment reimbursed for hATTR-PN.	—

FAP = familial amyloidotic polyneuropathy; hATTR amyloidosis = hereditary transthyretin-mediated amyloidosis; hATTR-PN = hereditary transthyretin-mediated amyloidosis with polyneuropathy; NYHA = New York Heart Association; PND = polyneuropathy disability.

Discussion Points

- The committee deliberated on vutrisiran considering the criteria for significant unmet need that are described in section 9.3.1 of the Procedures for CADTH Reimbursement Reviews. CDEC acknowledged the rarity of this condition; however, given that there are other treatment options currently available and reimbursed in most jurisdictions, CDEC concluded that the criteria allowing for additional uncertainty in the evidence were not met.
- CDEC heard from the clinical expert that among currently available treatments, patisiran is the most commonly used therapy in patients with hATTR-PN and is administered by IV every 3 weeks, with each infusion lasting [redacted]. CDEC acknowledged patient and clinical expert input expressing the need for effective treatments that offer a more convenient route of administration, less frequent dosing, improved patient access, and alleviation of caregiver burden. CDEC noted that vutrisiran, which is administered subcutaneously every 3 months, with each administration lasting [redacted], may address that need. However, CDEC concluded that there was no evidence that assesses the impact of vutrisiran's more convenient administration on efficacy outcomes.
- CDEC discussed that inotersen is another currently available treatment option for patients with hATTR-PN. Given the lack of robust comparative evidence between treatments for hATTR-PN, the choice between therapies is guided by considerations on availability, route and frequency of administration, patient preference, and contraindications. The sponsor's submitted comparative efficacy analyses of vutrisiran versus inotersen had significant limitations (including heterogeneity across study designs and populations, lack of comprehensive data to assess clinical heterogeneity,

and wide credible intervals), which meant that no firm conclusions could be drawn on the relative benefit of vutrisiran compared to inotersen.

- CDEC also discussed patients' desire for a lower risk of AEs, including falls. In the HELIOS-A trial, most AEs were mild or moderate in severity and a relatively small proportion of patients in both study groups discontinued treatment due to AEs. The clinical expert noted that the nature and type of AEs appeared consistent with those expected in this population and anticipated that the safety profile of vutrisiran would be similar to that of patisiran. Uncertainty regarding AEs remains in the absence of long-term safety data and relatively small sample sizes in the included studies.
- Given the heterogenous presentation of the disease, there is the potential for vutrisiran use in patients presenting with cardiac disease manifestations. All patients enrolled in the HELIOS-A trial had a New York Heart Association (NYHA) class of either I or II; patients with an NYHA class of III or IV were excluded from the study. The HELIOS-A trial was not designed to assess cardiac-specific efficacy outcomes; the impact of vutrisiran on cardiac biomarkers and echocardiographic parameters was assessed in exploratory analyses. Therefore, the potential benefit of vutrisiran on cardiac outcomes in patients with hATTR-PN remains uncertain.
- CDEC discussed the uncertainty in the number of patients who would be eligible for treatment with vutrisiran. The sponsor's estimated budget impact of reimbursing vutrisiran for hATTR-PN is based on the number of patients currently receiving treatment with patisiran or inotersen for hATTR-PN; however, based on prevalence estimates from the literature, the prevalence of hATTR-PN in Canada may be higher than estimated by the sponsor. Should the prevalence of hATTR-PN be higher than estimated, the budget impact of reimbursing vutrisiran will be greater.

Background

hATTR amyloidosis is a rare, autosomal-dominant, genetically inherited disease, characterized by mutations in the gene encoding TTR and multisystem extracellular deposition of amyloid that results in dysfunction of different organs and tissues.

hATTR amyloidosis often progresses rapidly and leads to worsening sensorimotor neuropathy, a condition that damages the patient's sensory and motor nerves, leading to escalating disability over time. Beyond sensorimotor neuropathy, the disease can also instigate a progressive autonomic neuropathy. This condition affects the nerves controlling the body's automatic functions, such as digestion, leading to gastrointestinal impairment, weight loss, and cachexia. The life expectancy of patients with hATTR-PN ranges from 10 to 15 years following the time of symptoms developing. Median survival from the time of diagnosis in hATTR-PN is 4.7 years.

While hATTR-PN is ultrarare, affecting an estimated 10,000 individuals globally, certain endemic regions like Portugal and Sweden exhibit higher prevalence rates (as high as 50 per 100,000 inhabitants). There is a lack of published Canadian prevalence estimates.

The disease also manifests as the cardiac variant known as ATTR-CM. In this form, TTR amyloid fibrils infiltrate the myocardium, leading to extracellular amyloid deposits and consequent restrictive cardiomyopathy and congestive heart failure. Symptoms are typical of restrictive cardiac disease, including dyspnea, orthostatic hypotension, and syncope.

Two treatments are authorized for market use in Canada for managing hATTR-PN: patisiran and inotersen. Both of these therapies have received positive CADTH recommendations with conditions. The mechanism of action of vutrisiran is the same as that of patisiran. Additionally, tafamidis, a TTR tetramer stabilizer, has been indicated for use in patients with hATTR amyloidosis who present primarily with cardiomyopathy. The primary goal of hATTR amyloidosis treatments is to decelerate disease progression, as there's no cure for reversing neuropathy.

Vutrisiran is indicated for the treatment of stage 1 or stage 2 polyneuropathy in adult patients with hATTR amyloidosis. The recommended dose of vutrisiran is 25 mg administered via subcutaneous injection once every 3 months. Vutrisiran has not been previously reviewed by CADTH.

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, multicentre study and 1 randomized, double-blind, placebo-controlled, multicentre study; both studies were in patients with stage 1 or stage 2 hATTR-PN
- patients' perspectives gathered by 1 patient group, TTR Amyloidosis Canada (TAC)
- input from the public drug plans and cancer agencies that participate in the CADTH review process
- input from 1 clinical specialist with expertise diagnosing and treating patients with hATTR-PN
- input from 1 clinician from the Amyloidosis Program of Calgary
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Stakeholder Perspectives

Patient Input

CADTH received 1 patient group submission from TAC. TAC is a non-for-profit organization dedicated to educating and supporting patients living with all forms of transthyretin amyloidosis. TAC primarily represents patients, caregivers, families, and some volunteer health workers in Canada, but also has members in the US, UK, and other European countries.

TAC provided input based on qualitative interviews conducted with patients who had experienced administration of both vutrisiran and patisiran. The interviewees mentioned that vutrisiran is more convenient than patisiran, as the administration is less frequent (every 3 months versus every 3 weeks), less time consuming (3 hours for the patisiran injection procedure plus travel time), and the root of administration

is subcutaneous rather than by IV. Patients stated that they were able to learn how to do a subcutaneous injection, which freed them from the burdens of relying on the infusion network, the necessities of preinjection therapy and clinic visits, the involvement of a caregiver in clinic visits, and missing a workday.

Furthermore, the interviewees found that vutrisiran may decrease the pharmacoeconomic burden of illness related to hATTR amyloidosis; avoiding the need for IV administration and being able to keep patients away from hospital centres may benefit an overburdened health system and patients who are frail and immunocompromised. Patients also believed that risk of falls may be lessened, which would lead to fewer hospital visits and a better maintenance of quality of life.

Clinician Input

Input From the Clinical Expert Consulted by CADTH

The primary goal of hATTR-PN treatments is to decelerate disease progression, as there is no cure for reversing neuropathy. Current treatments come with significant risks, and there's inconsistency in clinical outcomes between cardiac and neurologic responses. Moreover, there is a lack of comprehensive data on functional outcomes and overall patient quality of life, underscoring the unmet needs in this area.

According to the clinical expert consulted by CADTH, vutrisiran would likely be offered as first-line treatment to most patients with hATTR-PN. However, there's little evidence supporting its use for patients who have previously undergone a liver transplant, or for those who received other genetic therapies, like inotersen, or a comparable genetic therapy, like patisiran. While there's potential in combining therapies, evidence for treatment combinations is lacking. Vutrisiran might not revolutionize the treatment landscape but may offer enhanced convenience.

Vutrisiran is most effective for those with a confirmed hATTR amyloidosis diagnosis with established presence of neuropathy. The best patient candidates resemble those enrolled in the key clinical trials. Improved access to accurate and reliable testing would help in proper diagnosis. Though all patients with hATTR-PN might benefit, those with rapidly progressing neuropathy may experience the most significant improvements.

As noted by the clinical expert consulted by CADTH, treatment efficacy for hATTR-PN is evaluated using specific metrics, including mortality reduction and serious complication rates. Neuropathy outcomes, autonomic symptoms, and several neuropathy scales provide insights into disease progression and patient experience. Continuous clinical assessments ensure accurate monitoring of the patient's treatment response. In addition, it is common to monitor TTR levels in patients as part of monitoring response to treatment. Timing of assessments depends on the severity of the patient's disease (if asymptomatic or minimally symptomatic, yearly assessment is acceptable). In patients with more active disease, assessments every 3 or 6 months are appropriate.

According to the clinical expert consulted by CADTH, therapy might be halted when adverse effects outweigh the benefits. Decisions are based on patient tolerance and willingness, potential therapeutic efficacy, and if

neuropathy progression aligns with hATTR-PN's expected course. Treatment effectiveness is indicated by improvements in several neuropathic and autonomic symptoms.

Given the similarities with other neuromuscular conditions, it is optimal to have clinicians proficient in managing neuropathy patients as primary caregivers, according to the clinical expert consulted by CADTH. Care can be provided in hospitals or clinics with the right resources to address advanced neuropathy, including cardiac and autonomic symptoms.

Clinician Group Input

Input was received from 1 clinician from the Amyloidosis Program of Calgary. The clinician expressed that vutrisiran dosing and regimen present an improvement over those for currently approved patisiran in that treatment is only administered every 3 months, rather than every 3 weeks. In addition, the clinician noted that vutrisiran has the potential to improve patients' quality of life while attenuating disease progression.

Drug Program Input

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

Table 2: Responses to Questions From the Drug Programs

Implementation issues	Response
Relevant comparators	
One submitted trial (HELIOS-A) and an NMA support the comparable efficacy of vutrisiran and patisiran in patients with hATTR-PN. Alnylam is the market authorization holder for both Amvuttra (vutrisiran) and Onpattro (patisiran); advising that vutrisiran (SC every 3 months) is expected to replace patisiran (IV every 3 weeks) as the "standard of care" for hATTR-PN in Canada. Tegsedi (inotersen) is also a relevant comparator that was indicated by Health Canada for the treatment of hATTR-PN; its CADTH reimbursement criteria (December 2019) are identical to those of patisiran (July 2019).	Comment from the drug programs to inform CDEC deliberations.
Patisiran and inotersen are both reimbursed in the majority, but not all federal, provincial, and territorial jurisdictions.	Comment from the drug plans to inform CDEC deliberations.
Considerations for initiation of therapy	
The key inclusion and exclusion criteria for the HELIOS-A (vutrisiran) and APOLLO (patisiran) trials are the same. The CADTH reimbursement criteria for patisiran and inotersen are also same. Consider alignment with the initiation criteria for patisiran and inotersen, if appropriate. Are there any additional patient characteristics beyond disease diagnosis, scoring, or staging that should be considered for eligibility criteria for vutrisiran?	CDEC agreed with the clinical expert that the eligibility criteria of patisiran should also apply to vutrisiran. The clinical expert did not identify a rationale for applying additional or modified eligibility criteria to patisiran.

Implementation issues	Response
The pre-NOC indication and reimbursement request for vutrisiran is: For the treatment of hATTR amyloidosis in adults. The submitted trial (HELIOS-A) only evaluated vutrisiran for hATTR-PN. Given the heterogeneous nature of the disease, there is potential for vutrisiran to be used more broadly, including for patients with cardiomyopathy. Are there other patient subtypes that should be assessed for eligibility for vutrisiran, such as patients with: 1. hATTR cardiomyopathy 2. a confirmed genetic mutation but presymptomatic (patients in the HELIOS-A trial had FAP stage I and II disease at baseline) 3. advanced polyneuropathy (the HELIOS-A trial did not include any patients with FAP stage III disease at baseline) or previous liver transplant.	An NOC for vutrisiran was issued on October 18, 2023, with the following indication: AMVUTTRA (vutrisiran injection) is indicated for the treatment of stage 1 or stage 2 polyneuropathy in adult patients with hATTR amyloidosis. The sponsor updated their request for reimbursement to be per indication. The clinical expert suggested that evidence of efficacy of vutrisiran has limited generalizability to the following patient populations: • those with cardiomyopathy • those with advanced-stage polyneuropathies • those who have received a liver transplant • those with a confirmed genetic mutation who are presymptomatic. CDEC agreed with the clinical expert that there is no evidence to support the use of vutrisiran in these patients.
Considerations for continuation or renewal of therapy	
The primary end point in the HELIOS-A trial was the mNIS+7. In 2019, the clinical experts consulted for the CADTH reviews of patisiran and inotersen advised that the mNIS+7 is not used in clinical practice to monitor patients and that some components (i.e., quantitative sensory testing) are not available in all centres. There are no clearly defined renewal criteria for patisiran and inotersen. What objective measures can be employed to assess the efficacy of vutrisiran over time, ensuring ongoing reimbursement?	CDEC agreed with the clinical expert who suggested that similar approaches as the ones already in place for patients on patisiran should be implemented.
Considerations for discontinuation of therapy	
The discontinuation criteria for patisiran and inotersen include being permanently bedridden and dependent on assistance for basic activities of daily living or receiving end-of-life care. Consider alignment with the discontinuation criteria for patisiran and inotersen, if appropriate. Are there additional parameters that can be used to define loss of response, absence of clinical benefit, or disease progression specific to vutrisiran?	CDEC agreed with the clinical expert who suggested that similar discontinuation as the ones already in place for patients on patisiran criteria should be implemented.
Considerations for prescribing of therapy	
The product monograph notes that vutrisiran should be administered by a health care professional. There may be limited access to specialists with experience in the diagnosis and management of hATTR in some jurisdictions. • Is there evidence supporting the combination use of vutrisiran with other RNA-targeted treatments like inotersen or TTR stabilizers such as tafamidis for ATTR amyloidosis cardiomyopathy or diflunisal (i.e., off-label	The clinical expert noted that no current evidence exists to support the combination use of vutrisiran with other RNA-targeted treatments or TTR stabilizers. CDEC agreed with the clinical expert that it would be unlikely that such combination of treatments would be used.

Implementation issues	Response
use)? • Should patients who are already on another RNA-targeted treatment or TTR stabilizer be eligible for treatment with vutrisiran?	
Generalizability	
There is the potential for patients currently receiving patisiran (possibly inotersen) to be switched to vutrisiran. Is it appropriate for patients currently receiving patisiran (or possibly inotersen) to switch to vutrisiran?	CDEC agree with the clinical expert who did not anticipate any issues switching patients who were receiving patisiran (or possibly inotersen) to vutrisiran.
Care provision issues	
The product monograph notes that vutrisiran should be administered by a health care professional. The sponsor has indicated that vutrisiran will be imported, distributed, and administered through Innomar Strategies. Vutrisiran reduces serum vitamin A levels and vitamin A supplementation is advised. Genetic testing is required to confirm a diagnosis of hATTR amyloidosis and differentiate it from other causes of amyloidosis. Beyond administration by health care professionals, are there any additional concerns regarding the preparation, storage, administration, or dispensing of vutrisiran?	The clinical expert noted that while some patients may have a preference for infusions by health care professionals, most will likely be able to perform self-administration of SC vutrisiran or receive support from a family member to do so. CDEC agree with the clinical expert.
Regarding vitamin A supplementation due to reduced serum vitamin A levels caused by vutrisiran, are there specific recommendations or considerations for its administration?	CDEC agreed with the clinical expert who identified no additional recommendations beyond those implemented with patisiran.
System and economic issues	
Vutrisiran costs $143,041 per prefilled syringe. The sponsor's BIA indicates that vutrisiran is anticipated to be associated with a cost of $173 million over the 3-year forecast horizon; a net budget increase of $24 million over 3 years vs. the current scenario (patisiran and inotersen only).	Comment from the drug plans to inform CDEC deliberations.
Patisiran and inotersen have successfully completed price negotiations for hATTR-PN. Alnylam is the market authorization holder for patisiran — and is aware of its negotiated price.	Comment from the drug plans to inform CDEC deliberations.

ATTR amyloidosis = transthyretin-mediated amyloidosis; BIA = budget impact analysis; CDEC = CADTH Canadian Drug Expert Committee; FAP = familial amyloidotic polyneuropathy; hATTR amyloidosis = hereditary transthyretin-mediated amyloidosis; hATTR-PN = hereditary transthyretin-mediated amyloidosis with polyneuropathy; mNIS+7 = modified Neuropathy Impairment Score +7; NMA = network meta-analysis; NOC = Notice of Compliance; RNA = ribonucleic acid; SC = subcutaneous; vs. = versus.

Clinical Evidence

Systematic Review

Description of Studies

A sponsor-submitted systematic review identified 2 studies: HELIOS-A and APOLLO. HELIOS-A was a phase III, randomized, open-label, multicentre study that evaluated the efficacy and safety of vutrisiran over 18 months in patients with hATTR-PN. The study had 2 groups: a vutrisiran treatment group and a patisiran treatment group. The HELIOS-A study used an external placebo control from the APOLLO study to assess the efficacy of vutrisiran against placebo. Adults with hATTR amyloidosis (N = 164) were randomized 3:1 to receive vutrisiran 25 mg subcutaneous every 3 months or patisiran 0.3 mg/kg IV infusion every 3 weeks for 18 months. There were 2 HELIOS-A study sites in Canada, each with 1 patient (1 patient received vutrisiran, while the other received patisiran). The APOLLO study was a multinational, multicentre, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of patisiran over 18 months in patients with hATTR-PN. Adults with hATTR amyloidosis (N = 225) were randomized 2:1 to receive patisiran (0.3 mg/kg every 3 weeks by IV infusion for 18 months; n = 148) or placebo (normal saline; n = 77). Both trials had similar inclusion and exclusion criteria and outcomes definitions. Patients were diagnosed with hATTR-PN. Patients were excluded if they had advanced disease (mNIS+7 > 130) or if they had moderate cardiac involvement (NYHA > 2). In the HELIOS-A trial, the primary outcome measured the change in mNIS+7 of vutrisiran versus placebo at 9 months as per protocol and used as such for submissions to US, Japan, and Brazil. mNIS+7 at 18 months was considered the primary outcome for the EU and other regions. Secondary efficacy outcomes were planned with a hierarchical testing approach subsequent to the primary outcome of mNIS+7 at 9 months, these were mNIS+7 at 18 months, Norfolk QoL-DN score at 18 months, 10-metre walk test gait speed at 18 months, modified body mass index at 18 months, R-ODS score at 18 months, and the noninferiority of vutrisiran versus patisiran for TTR percent reduction at 18 months. The HELIOS-A trial explored the impact of vutrisiran on cardiac biomarkers and echocardiographic parameters in exploratory analyses.

In the HELIOS-A and APOLLO trials, 189 and 323 patients, respectively, were considered for randomization. The HELIOS-A study allocated 122 patients to vutrisiran and 42 to patisiran, while the APOLLO study allocated 77 patients to placebo and 148 to patisiran.

The median age in both trials was around 60 years; and the majority of participants were male and white. Similarly, most patients were diagnosed within 2 years of first symptom in both trials. Both trials had almost an equal allocation of patients with the V30M TTR genotype. More patients with a PND score of IIIA and IIIB were present in the APOLLO trial than in the HELIOS-A trial. Similarly, there were more patients with a NYHA classification of I and II in the APOLLO trial than in the HELIOS-A trial, where more than half of the patients had no signs of heart failure.

Efficacy Results

The PND score provides a measure of ambulatory function and polyneuropathy-related disability. Lower scores indicate greater ambulatory function and reduced disability. Change in PND score from baseline to

month 18 was an exploratory outcome in the HELIOS-A and APOLLO trials with no formal statistical testing. Overall, in the HELIOS-A trial, among the vutrisiran group (N = 122), [redacted]% ([redacted]) of patients showed improvement and [redacted]% ([redacted]) of patients exhibited no change. In the same trial, for the within-study patisiran group (N = 42), [redacted]% ([redacted]) of patients improved and [redacted]% ([redacted]) of patients had no change. Among the placebo group (N = 77) in the APOLLO trial, [redacted] and [redacted]% ([redacted]) of patients had no change.

The primary outcome in both trials was the change from baseline in mNIS+7. The mNIS+7 assesses the progression of the motor and the sensory aspects of polyneuropathy. A negative change versus a patient's own baseline represents neurologic improvement. In the HELIOS-A trial, among patients who contributed to the analysis at month 18, the vutrisiran group (N = 112) started with a baseline of 60.57 (standard deviation [SD] = 35.99) and exhibited a change of −0.46 (standard error of mean [SEM] = 1.60). The within-study patisiran group (N = 36) had a baseline of 57.68 (SD = 33.71) with a change of 1.53 (SEM = 2.59). Within the APOLLO trial placebo group (N = 51), patient baseline mNIS+7 was 74.61 (SD = 37.04) with a change of 28.09 (SEM = 2.28). The treatment difference in change from baseline for vutrisiran versus placebo (in the APOLLO trial) was −28.55 (95% CI, −34.00 to −23.10) in favour of vutrisiran.

The Norfolk QoL-DN score assesses 35 measures of symptoms and functional impairment related to nerve function, with higher scores indicating worse HRQoL. The 5 domains of the Norfolk QoL-DN are activities of daily living, physical function/large fibre neuropathy, small fibre neuropathy, symptoms, and autonomic neuropathy. In the HELIOS-A trial, the change in the vutrisiran group was −1.2 (SEM = 1.8) and −0.8 (SEM = 3.0) for the within-study patisiran group. In the APOLLO trial, the placebo group had a change of 19.8 (SEM = 2.6). The treatment difference of vutrisiran versus placebo (in the APOLLO trial) was −21.0 (95% CI, −27.1 to −14.9) in favour of vutrisiran. Norfolk QoL-DN score was a secondary outcome and was the second end point to be tested after the primary outcome. The presented results achieved statistical significance versus placebo.

The R-ODS is a 24-item scale used to assess the ability to perform everyday activities, with a lower score indicating worsening disability. In the HELIOS-A trial, the change from baseline for vutrisiran was −1.5 (SEM = 0.6) and was −1.3 (SEM = 0.9) for within-study patisiran. In the APOLLO trial, the placebo group showed a change of −9.9 (SEM = 0.8). The treatment difference of vutrisiran versus placebo (in the APOLLO study) was 8.4 (95% CI, 6.5 to 10.4) in favour of vutrisiran. R-ODS score was a secondary outcome and was the fifth end point to be tested in the testing hierarchy. All previous end points achieved statistical significance. Similarly, the results of R-ODS scores compared to placebo were statistically significant.

TTR is a tetrameric protein composed of 4 monomers. In the case of hATTR amyloidosis, the tetrameric protein destabilizes into unstable monomers and TTR fragments that can misfold and form amyloid fibril deposits in multiple organs, including the peripheral nervous system, heart, and gastrointestinal tract, leading to cellular injury and organ dysfunction with corresponding clinical manifestations. Serum TTR is considered a biomarker for vutrisiran's biological activity; however, no validated correlation with efficacy outcomes is available. The vutrisiran group exhibited an average reduction of [redacted]% (SD = [redacted]) from a baseline of [redacted] (SD = [redacted]). The within-study patisiran group showed an average reduction of [redacted]% (SD = [redacted]) from a baseline of [redacted] (SD = [redacted]). The vutrisiran group exhibited a median reduction of [redacted] (range, [redacted]) from a median

baseline of [redacted] (range, [redacted] to [redacted]). The within-study patisiran group showed a median reduction of [redacted] (range, [redacted] to [redacted]) from a median baseline of [redacted] (range, [redacted]). The median treatment group difference between vutrisiran and within-study patisiran was 5.28 (95% CI, 1.17 to 9.25). This outcome was the last end point in the testing hierarchy for the HELIOS-A trial. All previous end points achieved statistical significance. Vutrisiran met the prespecified 10% margin noninferiority criteria versus patisiran.

Post hoc analyses from the HELIOS-A trial were conducted for the primary and selected secondary efficacy outcomes comparing vutrisiran against within-study patisiran. For the mNIS+7 outcome, the post hoc least squares mean difference between vutrisiran and within-study patisiran at 18 months was −1.46 (95% CI, −7.36 to 4.43); for the Norfolk QoL-DN score outcome, the post hoc least squares mean difference was −1.6 (95% CI, −8.6 to 5.4); and for the R-ODS outcome, the least squares mean difference was 0.1 (95% CI, −2.0 and 2.2).

Harms Results

AEs from the HELIOS-A and APOLLO trials indicated a majority of participants experienced at least 1 such event after treatment with vutrisiran, patisiran, or placebo. In the HELIOS-A trial, 98% of patients treated with vutrisiran experienced AEs like falls, pain in the extremities, and diarrhea, among others; similar rates were seen for patisiran. In the APOLLO trial, both patients treated with patisiran (97%) and those in the placebo group (97%) reported AEs, including diarrhea, peripheral edema, and urinary tract infections. Serious adverse events (SAEs) varied between trials, with 26% of patients who received vutrisiran in the HELIOS-A trial experiencing at least 1 SAE and 43% of patients who received patisiran (in the HELIOS-A trial) experiencing at least 1 SAE. In the APOLLO study, 36% of patients who received patisiran and 40% of the placebo group reported at least 1 SAE. Treatment discontinuations due to AEs were noted in both trials, with deaths being a primary reason. Of all enrolled patients in the HELIOS-A trial, the number that died in each treatment group was 2% for vutrisiran and 7% for patisiran. In the APOLLO trial, 5% and 8% of patients died in the patisiran and placebo group, respectively. Notable harms included cardiac arrhythmias, experienced by 24.6% of patients in the vutrisiran group in the HELIOS-A trial, 7.1% of patients in the patisiran group in the same trial, 19% of patients in the patisiran group in the APOLLO trial, and 29% of patients in the placebo group in the APOLLO trial.

Critical Appraisal

The HELIOS-A trial used an external control, specifically the placebo group from the APOLLO trial. To infer whether the magnitude of the effect is attributable to the treatment when using an external control, the trials are typically required to have similar design and participant characteristics. In this setting, the HELIOS-A and APOLLO trials were aligned in terms of participant inclusion and exclusion criteria and outcome measures. Additionally, to help compare the response between the 2 trials, a patisiran group was included in the HELIOS-A trial. However, comparison of patient baseline characteristics indicated that patients in the APOLLO trial were at more advanced disease stages than those in the HELIOS-A trial. According to the clinical expert consulted by CADTH, this imbalance could impact treatment responses and the natural progression of the disease across the 2 trials. Overall, the extent and direction of the potential bias caused by imbalances in disease characteristic cannot be determined. To address potential imbalances in important

clinical baseline variables, the sponsor conducted a propensity score sensitivity analysis. While the results from the propensity score sensitivity analysis were supportive of the main finding, not all of the differences between the 2 studies could be addressed, including unmeasured or unrecognized factors. There were design differences between the HELIOS-A and APOLLO trials: HELIOS-A had an open-label design, whereas APOLLO used a double-blind approach. To mitigate biases from this difference, several data integrity strategies were employed in the HELIOS-A trial, such as restricting access to certain previous patient data or knowledge of treatment assignments by specific personnel. Despite these precautions, the potential for biases remained; however, the extent and direction of this potential bias cannot be determined.

A secondary end point in the HELIOS-A study was to test for the noninferiority of vutrisiran against patisiran in percent reduction in serum TTR protein levels. The sponsor established a noninferiority margin of 10% but no clear justification was available as to why 10% would be an acceptable noninferiority margin. However, considering that the 95% CI of the result of the end point was over the null and not close to the lower noninferiority margin, this limitation in clinical justification of the noninferiority margin is unlikely to affect the validity of the result.

The sponsor provided a number of post hoc analyses at the request of the European Medicines Agency, which compared the efficacy of vutrisiran to within-study patisiran in the HELIOS-A trial. While useful when considered in the context of the larger body of evidence, post hoc analyses have a number of limitations, including the lack of sufficient power to detect a difference, an inflated and uncontrolled type I error, and lack of an established noninferiority margin to test noninferiority. The post hoc analysis should be considered as supportive evidence.

The mNIS+7 is limited in its application to the Canadian clinical practice. The clinical expert consulted on this review provided feedback that the mNIS+7 instrument is not routinely used in Canadian clinical practice; instead, the COMPASS (Composite Autonomic Symptom Score) is more frequently used in clinical settings. While COMPASS was an outcome assessed in the APOLLO trial, it was not assessed in the HELIOS-A trial. The sponsor noted that mNIS+7 is not used in routine clinical assessment due to its complexity but provides a more comprehensive assessment of neuropathy, including manifestations of both peripheral and autonomic neuropathy. The mNIS+7 scale is a standard outcome used in clinical trials in the present therapeutic setting. The PND score is an applicable clinical measure. However, the findings of the PND score in the HELIOS-A and APOLLO trials were limited due to the exploratory nature of the outcome and the lack of formal comparative statistical testing. Mortality (deaths) was reported as part of the safety assessment of vutrisiran. However, the duration of the trial (18 months) is likely insufficient to adequately capture the full impact of treatment on patients' mortality. Hospitalizations, an additional clinically relevant outcome, was lacking in the available evidence.

The available evidence from the HELIOS-A trial with external placebo control from the APOLLO trial provides evidence of the efficacy of vutrisiran in patients with polyneuropathy. Both trials excluded patients in advanced disease stages. None of the studies included patients previously treated with TTR-lowering medications.

GRADE Summary of Findings and Certainty of the Evidence

Methods for Assessing the Certainty of the Evidence

For the pivotal studies (HELIOS-A and APOLLO) identified in the sponsor's systematic review, GRADE was used to assess the certainty of the evidence for outcomes considered most relevant to inform CADTH's expert committee deliberations, and a final certainty rating was determined as outlined by the GRADE Working Group.

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: mortality, hospitalization, PND score, mNIS+7, COMPASS 31, R-ODS score, Norfolk QoL-DN score, and TTR levels. No data were available for hospitalization and COMPASS 31.

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 a clinically important effect for Norfolk QoL-DN and R-ODS scores based on a threshold identified in the literature and/or informed by the clinical expert consulted by CADTH for this review. The target of the certainty of evidence assessment was the presence or absence of any (non-null) effect for mNIS+7, PND score, serum TTR, and mortality.

Table 3: Summary of Findings for Vutrisiran Versus Placebo (APOLLO) for Patients With hATTR Amyloidosis in the HELIOS-A Trial

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Placebo (APOLLO trial)	Vutrisiran (HELIOS-A trial)	Difference		
Neurologic impairment							
Percent of patients with PND score: 1. "improvement" 2. "no change" 3. "worsened" Follow-up: 18 months	199 (1 single-arm study with external control group)	NR	1. [redacted] 2. [redacted] 3. [redacted]	1. [redacted] 2. [redacted] 3. [redacted]	1. [redacted] 2. [redacted] 3. [redacted]	Low[a,c,f,g]	Vutrisiran may result in more patients with a PND score of "improvement" and "no change," and fewer patients with a score of "worsened" when compared with placebo. There is some uncertainty about the clinical importance of the estimates.
mNIS+7: LS mean (SE) change from baseline (0 [best] to 304 [worst]) Follow-up: 18 months	163 (1 single-arm study with external control group)	NR	28.09	−0.46 (1.60)	−28.55 (−34.00 to −23.10)	Low[a,c,f]	Vutrisiran may result in a decrease (improvement) in mNIS+7 when compared to placebo.
COMPASS 31: change from baseline Follow-up: 18 months	NA	No data available.	No data available.	No data available.	No data available.	NA	There is no evidence for the effect of vutrisiran on neurologic impairment (as measured by the COMPASS 31) when compared to placebo.
Functional impairment							
R-ODS score: LS mean (SE) change from baseline (48 [best] to 0 [worst]) Follow-up: 18 months	167 (1 single-arm study with external control group)	NR	−9.9	−1.5 (SE to 0.6)	8.4 (6.5 to 10.4)	Low[a,b,f]	Vutrisiran may result in a clinically important increase (improvement) in functional impairment measured by the R-ODS when compared to placebo.

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Placebo (APOLLO trial)	Vutrisiran (HELIOS-A trial)	Difference		
HRQoL							
Norfolk QoL-DN score: mean (SE) change from baseline (−4 [best] to 136 [worst]) Follow-up: 18 months	165 (1 single-arm study with external control group)	NR	19.8	−1.2 (SE to 1.8)	−21.0 (−27.1 to −14.9)	Low[a,d,f]	Vutrisiran may result in a clinically important decrease (improvement) in HRQoL measured with the Norfolk QoL-DN when compared to placebo.
Serum TTR							
Serum TTR: percent change from baseline, median	NA	No data available.	No data available.	No data available.	No data available.	NA	There is no evidence for the effect of vutrisiran on serum TTR when compared with placebo.
Harms							
Mortality Follow-up: 18 months	199 (1 single-arm study with external control group)	NR	[redacted]	[redacted]	[redacted]	Very low[e,f,g,h]	The evidence is very uncertain about the effects of vutrisiran on mortality vs. placebo.
Hospitalization Follow-up: 18 months	NA	No data available.	No data available.	No data available.	No data available.	NA	There is no evidence for the effect of vutrisiran on hospitalizations when compared with placebo.

CI = confidence interval; COMPASS 31 = Composite Autonomic Symptom Score 31; HRQoL = health-related quality of life; LS = least squares; mNIS+7 = modified Neuropathy Impairment Score +7; NA = not applicable; Norfolk QoL-DN = Norfolk Quality of Life–Diabetic Neuropathy; NR = not reported; PND = polyneuropathy disability; RCT = randomized controlled trial; R-ODS = Rasch-built Overall Disability Score; SD = standard deviation; SE = standard error; vs. = versus.

Note: Study limitations (which refer to internal validity or risk of bias), inconsistency across studies, 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 following footnotes.

[a]There was a risk of bias due to the open-label study design and the subjective nature of the outcome. The open-label study design may have biased measurement scores due to knowledge of assigned treatment, although the direction of the potential bias is unclear. The HELIOS-A study implemented integrity strategies for the mNIS+7 and Norfolk QoL-DN measures to mitigate any potential bias. The CADTH review team did not rate down for risk of bias, as, according to the CADTH review team's judgment, the potential risk of bias arising from the open-label study design did not warrant rating down to "very low" certainty.

[b]Imprecision was not rated down. No known threshold was identified but according to the clinical expert consulted by CADTH for the review, a 4-point difference between groups in the R-ODS score could be considered clinically meaningful. The CADTH review team judged that the effect estimate as well as both lower and upper boundaries of the 95%CI of the between-group difference exceeded the threshold and suggested a benefit. Despite the small sample size, the clinical expert consulted by CADTH judged the observed benefit with vutrisiran against placebo to be plausible and in line with what is observed with the comparator patisiran, with whom vutrisiran shares the same mechanism of action.

[c]Imprecision was not rated down. There is no known threshold and the clinical expert consulted by CADTH could not provide a threshold of important difference, so the null was used. The CADTH team judged that the point estimate and both the lower and upper boundaries of the 95% CI of the between-group comparison suggested a possibility of benefit. The treatment effect estimates observed in a small study sample may not be replicable in a larger study sample. However, the clinical expert consulted by CADTH judged the observed benefit with vutrisiran against placebo to be plausible and in line with what is observed with the comparator patisiran, with whom vutrisiran shares the same mechanism of action.

[d]Imprecision was not rated down. A threshold of 8.8 was identified in the literature. The CADTH review team judged that the effect estimate as well as both lower and upper boundaries of the 95%CI of the between-group difference exceeded the threshold and suggested a benefit. Despite the small sample size, the clinical expert consulted by CADTH judged the observed benefit with vutrisiran against placebo to be plausible and in line with what is observed with the comparator patisiran, with whom vutrisiran shares the same mechanism of action.

[e]Rated down 1 level for serious imprecision. There is no known threshold and the clinical expert consulted by CADTH could not provide a threshold of important difference. In the absence of a known threshold, the null was used. The CADTH review team judged that the point estimate for the between-group difference was unlikely to include an important effect; however, the lower bound of the 95% CI for the difference between groups suggested a possibility of little to no difference.

[f]The HELIOS-A study used an external control (placebo group in the APOLLO trial) in comparison to the vutrisiran group in the HELIOS-A trial. This observational comparison introduced the potential for bias resulting from confounding and selection bias and the certainty of evidence was started at low.

[g]This analysis was not part of the sponsor's statistical analysis plan and was requested by CADTH to facilitate a certainty of evidence appraisal.

[h]Rated down 1 level for serious indirectness due to insufficient duration of follow-up for the outcome according to clinical expert input.

Table 4: Summary of Findings for Vutrisiran Versus Patisiran for Patients With hATTR Amyloidosis in the HELIOS-A Trial

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Patisiran (within-study of the HELIOS-A trial)	Vutrisiran (HELIOS-A trial)	Difference		
Neurologic impairment							
Percent of patients with PND score 1. "improvement" 2. "no change" 3. "worsened" Follow-up: 18 months	164 (1 RCT)	NR	1. [redacted] 2. [redacted] 3. [redacted]	1. [redacted] 2. [redacted] 3. [redacted]	1. [redacted] 2. [redacted] 3. [redacted]	1. Low[d,f,h,i] 2. Very low[e,f,h,i] 3. Very low[e,f,h,i]	Vutrisiran may result in more patients with a PND score of "improvement" when compared with patisiran. The evidence is very uncertain about the effects of vutrisiran on the PND scores of "no change" and "worsened" vs. patisiran. There is some uncertainty about the clinical importance of the estimates.
mNIS+7: LS mean (SE) change from baseline (0 [best] to 304 [worst]) Follow-up: 18 months	148 (1 RCT)	NR	1.53	0.06 (SE to 1.48)	−1.46 (−7.36 to 4.43)	Moderate[a,f,i]	Vutrisiran likely results in little to no difference in mNIS+7 when compared to patisiran. There is some uncertainty about the clinical importance of the estimates.
Functional impairment							
R-ODS score: LS mean (SE) change from baseline (48	151 (1 RCT)	NR	−1.3	−1.2 (SE to 0.5)	0.1 (−2.0 to 2.2)	Moderate[b,f,i]	Vutrisiran likely results in little to no difference

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Patisiran (within-study of the HELIOS-A trial)	Vutrisiran (HELIOS-A trial)	Difference		
[best] to 0 [worst]) Follow-up: 18 months							in R-ODS scores when compared to patisiran.
HRQoL							
Norfolk QoL-DN score: mean (SE) change from baseline (−4 [best] to 136 [worst]) Follow-up: 18 months	149 (1 RCT)	NR	−0.8	−2.5 (SE to 1.8)	−1.6 (−8.6 to 5.4)	Moderate[c,f,i]	Vutrisiran likely results in little to no difference in Norfolk QoL-DN score when compared to patisiran.
Serum TTR							
Serum transthyretin: percent change from baseline, median Follow-up: 12 months (month 6 to month 18)	160 (1 RCT)	NR	[redacted]	[redacted] (NR)	5.28 (1.17 to 9.25)	High[g]	Vutrisiran results in little to no clinically important difference (i.e., a noninferior effect) for serum TTR when compared to patisiran.
Harms							
Mortality Follow-up: 18 months	164 (1 RCT)	NR	[redacted]	[redacted]	[redacted]	Very low[d,f,h,j]	The evidence is very uncertain about the effects of vutrisiran on mortality vs. patisiran.

CI = confidence interval; COMPASS 31 = Composite Autonomic Symptom Score 31; HRQoL = health-related quality of life; LS = least squares; mNIS+7 = modified Neuropathy Impairment Score +7; NA = not applicable; Norfolk QoL-DN = Norfolk Quality of Life–Diabetic Neuropathy; NR = not reported; PND = polyneuropathy disability; RCT = randomized controlled trial; R-ODS = Rasch-built Overall Disability Score; SD = standard deviation; SE = standard error; vs. = versus.

Note: Study limitations (which refer to internal validity or risk of bias), inconsistency across studies, 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 following footnotes.

[a]Imprecision was not rated down. The was no known minimal important difference and the clinical expert consulted by CADTH could not estimate a threshold of a clinically important difference. The CADTH team judged the point estimate and entire CI to suggest little to no difference.

[b]Imprecision was not rated down. No known threshold was identified but according to the clinical expert consulted by CADTH for the review, a 4-point difference between groups in R-ODS score could be considered clinically meaningful. The between-group difference and lower and upper bounds of the 95% CI did not meet the threshold, suggesting little to no difference.

[c]Imprecision was not rated down. A threshold of 8.8 was identified in the literature. The between-group difference and lower and upper bound of the 95% CI did not meet the threshold, suggesting little to no difference.

[d]Rated down 1 level for serious imprecision. There is no known threshold and the clinical expert consulted by CADTH could not provide a threshold of important difference, so the null was used. The CADTH team judged that the point estimate for the between-group difference as well as the upper bound of the 95% CI were likely to include an important benefit, while the lower bound of the 95% CI suggested little to no difference.

[e]Rated down 2 levels for very serious imprecision. There is no established minimal important difference and the clinical expert consulted by CADTH could not provide a threshold of important difference. In the absence of a known threshold, the null was used. The CADTH review team judged that the point estimate for the between-group difference was unlikely to include an important effect; however, the upper and lower bounds of the 95% CI for difference between groups suggested a possibility of both benefit and harm.

[f]Rate down 1 level for serious risk of bias due to the analyses being post hoc and not part of the protocol and may have been chosen among many potential analyses of the data.

[g]Imprecision was not rated down. The clinical expert consulted by CADTH could not provide a threshold of important difference. The noninferiority margin set out in the HERLIOS-A trial was used as the threshold. The CADTH review team judged that the point estimate and both the lower and upper boundaries of the 95% CI of the between-group comparison suggested little to no difference; the 95% CI excluded the noninferiority margin (10%).

[h]This analysis was not part of the sponsor's statistical analysis plan and was requested by CADTH to facilitate a certainty of evidence appraisal.

[i]There was a risk of bias due to open-label study design and the subjective nature of the outcome. The open-label study design may have biased measurement scores due to knowledge of assigned treatment, although the direction of potential bias is unclear. HELIOS-A implemented integrity strategies for the mNIS+7 and Norfolk QoL-DN measures to mitigate any potential bias. CADTH review team did not rate down for risk of bias, as it was believed that rating down 1 time due to the post hoc nature of the analyses was adequate to account for risk of bias concerns.

[j]Rated down 1 level for serious indirectness due to insufficient duration of follow-up for the outcome according to clinical expert input.

Economic Evidence

Cost and Cost-Effectiveness

Table 5: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Markov model
Target population	Adults with hATTR-PN
Treatment	Vutrisiran
Dose regimen	25 mg once every 3 months via SC injection
Submitted price	$143,041 per 0.5 mL vial
Treatment cost	Annual per-patient cost of $572,164
Comparators	Patisiran Inotersen
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (40 years)
Key data source	Network meta-analysis; efficacy of vutrisiran informed by the HELIOS-A trial
Key limitations	• It is uncertain whether vutrisiran provides a clinical benefit relative to patisiran or inotersen for hATTR-PN owing to uncertainty in the clinical evidence submitted by the sponsor. The CADTH clinical review concluded that the efficacy of vutrisiran is likely similar to patisiran (overall moderate certainty of evidence), while limitations in the sponsor-submitted NMA preclude meaningful conclusions from being drawn for the efficacy of vutrisiran vs. inotersen. • The impact of AEs on the cost-effectiveness of vutrisiran was not adequately explored in the sponsor's base case owing to the use of naive comparisons and the inclusion of only "treatment-related" AEs. • The sponsor included in their model a benefit associated with SC administration vs. IV administration based on the assumption that less frequent and less invasive treatment will have a reduced negative impact on patients' HRQoL. Approximately 98% of the incremental QALYs gained with vutrisiran relative to patisiran were owing to differences in administration route and frequency. The magnitude of any HRQoL benefit that patients may experience because of receiving treatment less frequently and by less invasive means is highly uncertain. • The long-term efficacy of vutrisiran is uncertain owing to a lack of clinical data beyond 18 months. Potential waning of effectiveness was not explored. • The survival benefit predicted for vutrisiran (incremental 0.07 and 3.26 LYs relative to patisiran and inotersen, respectively) is highly uncertain. • The model structure, based on PND score, does not adequately reflect hATTR-PN, in that it does not capture autonomic symptoms associated with hATTR amyloidosis (e.g., pain, gastrointestinal symptoms). The validity, reliability, and responsiveness of PND scores to change have not been investigated in patients with hATTR-PN.

Component	Description
CADTH reanalysis results	• Given the limitations identified within the sponsor's economic analysis, CADTH was unable to provide a more reliable estimate of the cost-effectiveness of vutrisiran. Based on the sponsor's analysis, vutrisiran is not a cost-effective treatment option for hATTR-PN at a willingness-to-pay threshold of $50,000 per QALY gained. The probability of vutrisiran being the optimal treatment was 0% in the sponsor's analysis. • There is insufficient clinical evidence to justify a price premium for vutrisiran over the currently available treatments for hATTR-PN. To ensure cost-effectiveness, vutrisiran should be no more costly than the lowest-cost funded treatment used for hATTR-PN.

AE = adverse event; hATTR amyloidosis = hereditary transthyretin-mediated amyloidosis; hATTR-PN = hereditary transthyretin-mediated amyloidosis with polyneuropathy; HRQoL = health-related quality of life; LY = life-year; NMA = network meta-analysis; PND = polyneuropathy disability; QALY = quality-adjusted life-year; SC = subcutaneous; vs. = versus.

Budget Impact

CADTH identified the following key limitations with the sponsor's analysis: uncertainty in the number of patients with hATTR-PN eligible for vutrisiran and uncertainty in the price of drugs paid for by public drug plans. In the absence of more reliable input values related to the eligible population size, the sponsor's base case was maintained. The net budget impact of reimbursing vutrisiran was estimated by the sponsor to be $4,793,861 in year 1, $8,173,140 in year 2, and $10,845,128 in year 3, for a 3-year incremental cost of $23,812,130. The estimated budget impact is highly sensitive to the number of patients eligible for vutrisiran and reflects its use only by patients with hATTR-PN.

The sponsor is the market authorization holder for both vutrisiran and patisiran and has indicated that vutrisiran will replace patisiran. The sponsor's budget impact analysis is based on the publicly available list price of patisiran and does not consider the negotiated confidential price of patisiran.

CDEC Information

Members of the Committee

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

Meeting date: November 23, 2023

Regrets: One expert committee member did not attend.

Conflicts of interest: None

ISSN: 2563-6596

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.