CADTH

CADTH COMMON DRUG REVIEW

Pharmacoeconomic Review Report

Patisiran (Onpattro)

(Alnylam Netherlands B.V.)

Indication: Treatment of polyneuropathy in adult patients with hereditary transthyretin-mediated amyloidosis.

Service Line:	CADTH Common Drug Review
Version:	Final (With Redactions)
Publication Date:	August 2019
Report Length:	42 Pages

CADTH

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

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

CADTH

Table of Contents

Tables

Figures

Abbreviations

AE	adverse event
BSC	best supportive care
CI	confidence interval
CORD	Canadian Organization for Rare Disorders
ED	extended dominance
hATTR	hereditary transthyretin-mediated
ICUR	incremental cost-utility ratio
NT-proBNP	N-terminal prohormone brain-type natriuretic peptide
OLT	orthotopic liver transplant
PND	polyneuropathy disability
QALY	quality-adjusted life-year
V122I	valine to isoleucine substitution at position 122
V30M	valine to methionine substitution at position 30

Table 1: Summary of the Manufacturer's Economic Submission

Drug Product	Patisiran (Onpattro)
Study Question	**Base-case analysis:** From the perspective of the publicly funded health care payer, what is the incremental cost-effectiveness of patisiran **compared with inotersen** for the treatment of polyneuropathy in adult patients with hereditary transthyretin-mediated amyloidosis (hATTR) in Canada? **Scenario analysis:** From the perspective of the publicly funded health care payer, what is the incremental cost-effectiveness of patisiran **compared with best supportive care** for the treatment of polyneuropathy in adult patients hATTR in Canada?
Type of Economic Evaluation	Cost-utility analysis
Target Population	Adult patients with hATTR with polyneuropathy
Treatment	Patisiran, administered by infusion at a 0.3 mg/kg dose (to a maximum of 30 mg) once every 3 weeks
Outcome	QALYs
Comparators	• Inotersen • BSC, consisting of supportive care medication
Perspective	Canadian publicly funded health care payer
Time Horizon	Lifetime (20 years)
Results for Base Case	Patisiran was: • less costly and more effective than inotersen (dominant) • associated with an ICUR of $736,818 per QALY gained compared with BSC.
Key Limitations	CDR identified several key limitations with the submitted analysis: • Different approaches were used to calculate the efficacy of patisiran, depending on the comparator selected. Therefore, for an identical patient population, the efficacy of patisiran would differ based on the comparator. This is inappropriate and does not adhere to best practices. Consequently, results could not be reported sequentially. • The health states within the model did not comprehensively reflect the clinical progression and the effects of treatment, resulting in the application of treatment-specific utility values and health state costs. • The inclusion of caregiver disutility does not align with the specified perspective of the analysis (public payer perspective). • Health state costs were derived from resource use estimates from a Delphi panel of physicians with experience managing patients in the UK. The generalizability of resource use from the UK to a Canadian setting is uncertain. The manufacturer also included costs that would not be covered by Canadian public health care payers, resulting in higher health state costs that favour patisiran. • The cardiovascular benefits of patisiran are uncertain. Although captured in the economic model based on the findings of the APOLLO trial prognostic imbalance was noted on baseline cardiovascular disorders between treatment arms. • Uncertainty exists in the price of inotersen as no public pricing was available at the time of the review.

CDR Estimate(s)	A sequential analysis was undertaken by CADTH, applying the relative effects of inotersen from the manufacturer's indirect comparison with the trial results of patisiran and BSC. CADTH also adjusted model inputs to meet recommendations outlined in the CADTH economic guidelines — for example, use of Canadian health care resources, treatment effects based on evidence from the clinical review, the removal of treatment-specific utilities and resource use, and updated Canadian prices. • In the sequential analysis, inotersen was extendedly dominated by patisiran and the incremental cost-utility ratio of patisiran compared with BSC was $4,818,778 per additional QALY. • A price reduction of 98% is required for patisiran to be cost-effective compared with BSC (defined at a willingness-to-pay threshold of $50,000 per QALY).

BSC = best supportive care; CDR = CADTH Common Drug Review; hATTR = hereditary transthyretin-mediated amyloidosis; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.

Drug	patisiran (Onpattro)
Indication	For the treatment of polyneuropathy in adult patients with hereditary transthyretin-mediated amyloidosis
Listing Request	As per indication
Dosage Form	2 mg/mL; 5 mL solution in a single-use 10 mL vial
NOC Date	June 8, 2019
Manufacturer	Alnylam Netherlands B.V.

Executive Summary

Background

Patisiran (Onpattro) is indicated for the treatment of polyneuropathy in adult patients with hereditary transthyretin-mediated amyloidosis.[1] Patisiran is administered through IV infusion at a dosage of 0.3 mg per kg of body weight once every three weeks up to a recommended maximum dose of 30 mg.[1] Patisiran is supplied in single-use 2 mg/mL 10 mL vials at a cost of $13,022.02 per vial.[2] The annual cost is between $451,430 and $677,145 per patient, depending on whether two vials (for those between 34 kg and 66 kg) or three vials (for those greater than 66 kg) are required, respectively.

The manufacturer submitted a cost-utility analysis of patisiran compared with inotersen in its base case and compared with best supportive care (BSC) in a scenario analysis.[2] The goal of BSC is symptomatic management and may include treatments for polyneuropathy, gastrointestinal disorders, and bladder dysfunction such as pregabalin, metronidazole, and anticholinergics. The analysis was conducted from the perspective of the Canadian publicly funded health care payer over a lifetime horizon (20 years), with cycles defined as every six months. Future costs and benefits were discounted at 1.5%.[2] The manufacturers used a Markov cohort model with health states defined by polyneuropathy disability (PND) scores, N-terminal prohormone brain-type natriuretic peptide (NT-proBNP) levels (greater than or equal to 3,000 pg/mL was associated with higher cardiac involvement), orthotopic liver transplant, and death.[2] Transition probabilities comparing patisiran with inotersen were estimated from the manufacturer's indirect comparison.[3] Transition probabilities comparing patisiran with BSC were estimated directly from the APOLLO trial, which investigated the safety and efficacy of patisiran.[4] Utilities for each health state were estimated by regression of the EuroQol 5-Dimensions questionnaire data from the APOLLO trial, with treatment and time as covariates of the regression.[2] Costs included drug-related costs (including administration, adverse events, pre-medications for patisiran, and monitoring), liver transplant, end-of-life care, and health state costs.[2] The health state costs were derived using resource use elicited from a survey of UK physicians experienced in treating hereditary transthyretin-mediated amyloidosis patients for each PND stage; and included wheelchairs, home adjustments, dental care, and acupuncture.[2]

The manufacturer reported that patisiran dominated inotersen (patisiran was less costly and more effective). Compared with BSC, patisiran was associated with an incremental cost-utility ratio (ICUR) of $736,818 per quality-adjusted life-year (QALY) gained.[2] Under this

scenario analysis, patisiran had a 0% probability of being the most likely cost-effective intervention at a willingness-to-pay threshold of $50,000 per QALY.[2]

Summary of Identified Limitations and Key Results

The CADTH Common Drug Review identified several key limitations with the model submitted by the manufacturer.

Different estimates of the efficacy of patisiran were used in the model, depending on which comparator was selected for the analysis. This resulted in different estimated costs and QALYs of patisiran, depending on whether it was compared with inotersen or BSC. This also meant it was not possible to consider all comparators together in a single analysis so that a sequential analysis could be run to meet CADTH guidelines.[5] CADTH requested that the manufacturer correct this, but the manufacturer stated that this was not possible.[6]

The progression of polyneuropathy was described by the manufacturer in its economic model using the PND scale, a functional scale that measures ambulatory ability.[7] As such, the manufacturer's model did not capture important patient outcomes — namely, aspects of the disease course associated with autonomic dysfunction. This resulted in the application of utility values and health state costs that differed by treatment to account for differences in these aspects. Further concerns exist with the health state costs, as they reflect clinical practice within the UK and may not be representative of a Canadian setting. As such, the types of resources captured in the health state cost calculation included costs that would not be generally covered by a Canadian public health care payer. Caregiver disutilities were also applied, which misaligns with the perspective of the analysis.

The manufacturer also made some optimistic assumptions in favour of patisiran. They assumed that patients on patisiran would have the same change in NT-proBNP beyond the clinical trial (extrapolation period) as observed in the clinical trial (efficacy period), compared with inotersen and BSC, which were assumed to do much worse in the extrapolation period than in the efficacy period. The cardiovascular benefit included in the economic model for patients on patisiran is uncertain, given that it was based on the findings of the APOLLO trial. Specifically, prognostic imbalance was noted within this study as patients in the placebo arm had higher rates of cardiovascular disorders at baseline. In addition, although Health Canada approved a dosage of 0.3 mg per kg of body weight every three weeks,[1] a lower treatment cost was assumed based on the assumption that adherence would not be 100% for patients receiving patisiran, whereas the adherence on inotersen would be 100%. Another limitation was that the Canadian price for inotersen was unknown at the time of this review. In the manufacturer's submitted model, the maximum international reference drug price for inotersen was applied, which may have overestimated the drug costs of inotersen, favouring patisiran.[2]

CADTH attempted to address some of these limitations. To facilitate a sequential analysis, the transition matrix for inotersen was calculated by applying the relative effect of inotersen from the indirect treatment comparison directly with the APOLLO trial results. In addition, CADTH's modification to the manufacturer's model included assuming no difference in NT-proBNP progression, using the same utility values for health states, eliminating the utility associated with a caregiver, using the same rate of treatment adherence as inotersen (i.e., 100%), removing health care resources not covered by Canadian public health care payers, and updating administration and liver transplant costs. In the CADTH reanalyses, the estimated price of inotersen was based on calculating the relative price between patisiran and inotersen in other non-Canadian jurisdictions (see Appendix 1).

Based on CADTH reanalyses, BSC had the lowest lifetime costs at $371,029 and QALYs of 3.65, compared with costs of $4,953,048 and 3.69 QALYs for inotersen, and $5,059,913 and 4.62 QALYs for patisiran. This resulted in inotersen being extendedly dominated and patisiran having an ICUR of $4,818,778 per additional QALY compared with BSC.

Conclusions

The key limitations of the manufacturer's analysis include the use of different estimates of efficacy for patisiran depending on the comparator (which made considering all comparators within one analysis problematic uncertain) and optimistic cardiovascular benefit assumed for patisiran, the application of treatment-specific health state utilities, and the inclusion of health care resources not covered by Canadian public health care payers. CADTH found that the results were sensitive to the identified limitations. CADTH reanalysis estimated the ICUR for patisiran to be $4,818,778 per additional QALY compared with BSC. A price reduction of 98% would be required for the ICUR for patisiran to fall below the $50,000 per QALY threshold compared with BSC.

The economic findings require cautious interpretation, especially given the uncertainty in the true price of inotersen.

Information on the Pharmacoeconomic Submission

Summary of the Manufacturer's Pharmacoeconomic Submission

The manufacturer submitted a cost-utility analysis comparing, in the base case, patisiran with inotersen and, in a scenario analysis, patisiran with best supportive care (BSC) for the treatment of polyneuropathy in adult patients with hereditary transthyretin-mediated (hATTR) amyloidosis.[2] BSC was comprised of therapies directed to address specific symptoms rather than targeted at altering the underlying disease and may include drugs such as tramadol and pregabalin to manage the symptoms of polyneuropathy, metronidazole for gastrointestinal disorders, anticholinergics and tolterodine for bladder dysfunction, procedures such as catheterization and colostomies, and primary care. The model used a lifetime horizon (20 years) from the perspective of the publicly funded Canadian health care payer with costs and clinical outcomes (quality-adjusted life-years [QALYs]) discounted at 1.5% per annum.[2] The manufacturer assumed all patients, regardless of disease stage, would be eligible to receive patisiran.[2] The manufacturer stated that the model reflected a population that had baseline characteristics reported from the APOLLO trial (70.5% males, average age: 58.8).[4]

Model Structure

A Markov model was submitted by the manufacturer with 14 living health states that measured hATTR amyloidosis disease progression combining polyneuropathy and cardiac outcomes, along with the possibility of receiving an orthotopic liver transplant (OLT), and death as the absorbing health state.[2]

To characterize progression of polyneuropathy, health states in the model were defined based on polyneuropathy disability (PND) scores, with six stages:

- PND 0, no symptoms
- PND I, sensory disturbances in extremities but preserved walking capability
- PND II, difficulties walking but without the need for a walking stick
- PND IIIA, walking with the help of one stick or crutch
- PND IIIB, walking with the help of two sticks or crutches
- PND IV, patient confined to a wheelchair or a bed.

Within the polyneuropathy stages, patients were further stratified between those with the cardiac biomarker N-terminal prohormone brain-type natriuretic peptide (NT-proBNP) less than 3,000 pg per mL and those with NT-proBNP greater than or equal to 3,000 pg per mL as an indicator of cardiac involvement.[2] At the third cycle (corresponding to a wait time of 14 months), patients in PND I and NT-proBNP less than 3,000 pg per mL may transition to the OLT health state and thereafter remain in the post-OLT health state.[2] Death can occur while in any of the 14 living health states.[2]

Patients entered the model distributed across the NT-proBNP and PND I to IIIB health states according to the APOLLO trial's baseline distributions. The inclusion criteria for APOLLO excluded patients in the PND 0 and PND IV health states.[2] In each six-month cycle, patients

may remain in the same health state, or transition to a less or more severe health state. Therefore, patients in PND I who improve would transition to PND 0 while patients who worsen may transition to PND II, PND IIIA, PND IIIB, or PND IV. In the comparison with inotersen, transition probabilities for patisiran and inotersen were estimated from the manufacturer's submitted indirect treatment comparison involving two pivotal trials: the APOLLO study for patisiran and the NEURO-TTR study for inotersen.[8,9] Transition probabilities for patisiran and BSC were estimated directly from the APOLLO trial. Treatment efficacy was separated into the efficacy period (initial 18 months, corresponding to the duration of the APOLLO trial) and the extrapolation period. It was assumed patisiran would have the same treatment efficacy in both the efficacy and extrapolation periods while patients on inotersen or BSC would have cardiac outcomes in the extrapolation period that were worse than in the efficacy period.[2] It was assumed that 2.5% of patients who would be eligible for OLT (i.e., PND I and NT-proBNP less than 3,000 pg per mL) would receive OLT in the third cycle of the model and treatment by patisiran or inotersen would discontinue. Of these patients, 29.6% would experience PND progression.[2] Excess mortality was based on NT-proBNP strata and OLT health states.[2]

Utilities within the manufacturer's model were derived from a regression of EuroQol 5-Dimensions questionnaire data from the APOLLO study across all available time points, using a Canadian value set and stratified by PND.[2] By incorporating treatment and time as covariates to the regression, the manufacturer's approach resulted in patients on patisiran improving over time and patients on BSC worsening over time, even within the same health state. [redacted] A decrement in utility of 0.125 was also applied to patients in PND IV to capture the caregiver burden associated with severe disease.[2] Utilities due to adverse events (AEs) were not included to avoid double counting since treatment-specific utilities were already used. AEs were selected if their occurrence was more than 2% in each arm of the APOLLO trial and the incidence was informed directly from this study for patisiran and BSC. For inotersen, only severe AEs that were also recorded in the APOLLO trial were included; these were sourced from the NEURO-TTR trial. AEs were accounted for in the manufacturer's economic model as costs.[2]

The model included drug-related costs (i.e., acquisition, administration, monitoring, and management of AEs), medical costs relating to PND health states, costs related to liver transplant, and end-of-life costs. Drug costs for patisiran were provided by the manufacturer. The modelled drug costs assumed no vial sharing and were based on the average number of vials used in the APOLLO trial ([redacted]% of patients used two vials and [redacted]% of patients used three vials).[2] No drug price was available for inotersen at the time of this review so the manufacturer estimated its cost by taking the maximum international prices from Germany and the US and converting this to Canadian values based on exchange rates (i.e., $11,282.675 per 300 mg).[2] Health state costs were derived using resource use elicited from a survey of UK physicians experienced in treating hATTR amyloidosis patients for each PND stage; and included wheelchairs, home adjustments, dental care, and acupuncture.[2]

Manufacturer's Base Case

The manufacturer reported the results separately for the base case and the scenario analysis with no incremental analysis conducted to compare patisiran, inotersen, and BSC together. Patisiran was found by the manufacturer to be $323,476 less expensive than inotersen and $4,691,405 more expensive than BSC. The estimated benefit of patisiran was an additional 3.76 QALYs compared with inotersen and 6.37 QALYs compared with BSC. Table 2 shows the contribution of the different sources of cost to the overall total costs. In the manufacturer's analysis, patisiran dominated inotersen (patisiran was less costly and more effective) and the incremental cost-utility ratio (ICUR) of patisiran compared with BSC was $736,818 per additional QALY gained.[2]

Table 2: Summary of Results of the Manufacturer's Base Case

	Comparison With Inotersen			Comparison With BSC		
	Patisiran (a)	Inotersen (b)	Difference (a − b)	Patisiran (d)	BSC (e)	Difference (d − e)
QALYs	6.60	2.85	3.76	7.14	0.78	6.37
LY	10.75	8.69	2.06	NR	NR	NR
Cost ($)						
Drug Acquisition Costs	5,576,110	5,092,357	483,753[a]	NR	NR	NR
Other Medical Costs	1,303	1,074	229[a]	NR	NR	NR
Adverse Event Costs	9,038	2,978	6,060[a]	NR	NR	NR
Administration Costs	90,056	3,051	87,005[a]	NR	NR	NR
End-of-Life Costs	5,255	6,045	−790[a]	NR	NR	NR
Liver Transplant Costs	1,777	1,079	698[a]	NR	NR	NR
Health State Costs	389,586	1,290,016	−900,430[a]	NR	NR	NR
Total Costs	6,073,125	6,396,601	−323,476	5,935,174	1,243,769	4,691,405
($/QALY)			Dominant			736,818

BSC = best supportive care; LY = life-years; NR = not reported; QALY = quality-adjusted life-year.

[a] Not reported but calculated from manufacturer's model.

Source: Manufacturer's pharmacoeconomic submission.[2]

Summary of Manufacturer's Sensitivity Analyses

Uncertainty was addressed using scenario analyses. The manufacturer tested:

- different indirect comparison results, using the Bucher method
- different assumptions for missing data
- the assumption that the utilities associated with inotersen worsen over time.

All of the manufacturer's scenario analyses comparing patisiran with inotersen resulted in patisiran dominating inotersen. All of the manufacturer's scenario analyses comparing patisiran with BSC resulted in patisiran having an ICUR greater than $500,000 per QALY gained.[2]

The results of these analyses suggest that the parameters tested by the manufacturer did not have an impact on the model's results.

Limitations of Manufacturer's Submission

1) **Different approaches were taken to estimate the effect of patisiran depending on the comparator:** When compared with BSC, patisiran has a higher estimated number of QALYs than when compared with inotersen, as reported in Table 2. This was due to the fact that different methodological approaches were used to derive the model's efficacy inputs depending on the comparator. Yet, for an identical starting patient cohort, having differing effectiveness of patisiran that depends on the comparator selected has limited clinical validity. The comparison of patisiran with inotersen was based on the manufacturer's indirect comparison.[3] This comparison estimated the relative risk of response for patisiran compared to inotersen. Using the estimated relative risk, the manufacturer developed a transition matrix based on the trivariate transition outcomes (improve, remain stable, or progress) that assumed patients' progress between adjacent health states. The comparison of patisiran with BSC was based directly on the clinical trial's results and allowed patients to progress to any health state.[8] Given that different approaches were used to calculate the transition matrix, it is difficult to undertake incremental analysis as recommended by CADTH guidelines.[5] Instead, the manufacturer presented separate pairwise comparisons with inotersen and BSC. CADTH requested that the manufacturer correct this, but the manufacturer stated that this was not possible.[6]

2) **The health states used in the model did not capture all aspects of the condition:** To describe disease progression, health states in the model were defined by PND scores.[2] PND scores are based only on mobility impairment and do not capture autonomic symptoms associated with hATTR amyloidosis. hATTR amyloidosis is a multi-faceted disease that causes motor, sensory, and autonomic neuropathy, which leads to progressive muscle weakness and disability, pain, wasting, gastrointestinal symptoms, and other autonomic symptoms, such as orthostatic hypotension.[7] To compensate for the inability of the model to capture all health changes through its health states, the manufacturer used treatment-specific utility values and costs.

   The EuroQol 5-Dimensions data were collected in the APOLLO trial and utilities were estimated using the Canadian value set.[2] For the comparison with BSC, linear regression on utilities was undertaken to estimate the utility by PND score, controlling for treatment and time. Maximum and minimum utility values were used to constrain the values used in the model since the linear nature of the regression model would otherwise allow utility values outside expected bounds (e.g., better than perfect health).[2] For the comparison with inotersen, it was assumed that inotersen had a fixed utility reduction compared with patisiran. [redacted] The use of treatment-specific utility values is contradictory to CADTH guidelines that recommend that utilities be associated with health states.[5]

   Similarly, the manufacturer assumed that patients on patisiran would have a [redacted]% reduction in health state costs relating to polyneuropathy and a [redacted]% reduction in health state costs relating to cardiomyopathy.[2] These reductions were based on a Delphi process undertaken with UK clinicians. When asked about the extent to which they expected health care costs to change for patients with hATTR amyloidosis if patisiran were introduced, five of these clinicians reported that they would expect a 50%

reduction in polyneuropathy-related health care use and two reported that they would expect a 25% reduction. For cardiomyopathy, three clinicians expected a 50% reduction, two expected a 25% reduction, and one expected a 0% reduction.[2] A weighted average was estimated by the manufacturer, resulting in a [redacted]% reduction in polyneuropathy-related costs and a [redacted]% reduction in cardiomyopathy-related costs due to patisiran. These values were then assumed to affect patients receiving patisiran at any given PND score and NT-proBNP level. Those receiving inotersen had no change in health state costs.[2] According to the clinical experts consulted by CADTH for this review, patients in the same health state but receiving different treatments may consume fewer health care resources due to differences in AEs or drug administration, both of which are already captured.

The application of drug-specific health state costs and utilities would favour patisiran as it would produce higher expected utilities and lower expected costs.

3) **Caregiver impacts incorporated into base case not appropriate for the public payer perspective:** The manufacturer included caregiver disutilities, which are not applicable to the public payer perspective. The inclusion of caregiver disutilities would be suitable under a societal perspective.[2] A caregiver disutility was applied in the manufacturer's base case to all patients in PND IV. This assumption would favour patisiran, as patients on patisiran progress more slowly to PND IV and would have higher expected QALYs compared with patients on inotersen or BSC.

4) **Health state costs may not be representative of Canadian public payers:** The stated objective of the Delphi process undertaken by the manufacturer was to "investigate current use of UK National Health Service (NHS) and Personal and Social Services (PSS) resources in hATTR amyloidosis."[2] The resource use was combined with unit costs from Canadian sources.[2] However, this conversion does not take into account the differences in treatment practices between Canada and the UK. Furthermore, the UK system includes care that would normally not be covered by most Canadian public health care payers, including dental care costs, acupuncture, physiotherapy, and allied care. The costs captured in the manufacturer's model extended to walking frames, sticks, wheelchairs, and home renovations in which reimbursement varies by Canadian jurisdiction. The inclusion of these costs resulted in PND IV health state costs of $198,000 annually.

5) **Claims on the treatment effect of patisiran on cardiac-related outcomes is uncertain:** As discussed in the clinical review, the evidence of an effect of patisiran on cardiac outcomes was limited. Although some cardiac biomarkers were measured as exploratory outcomes, it is unclear if these measures represent direct clinical benefit. The clinical review further noted differences between groups at baseline in terms of the proportion of patients with a history of cardiac disease, or that met the study's criteria for pre-existing cardiac amyloid involvement (placebo, 47%; patisiran, 61%). These baseline differences make it difficult to interpret the cardiac data presented. It was also reported that there was a planned statistical analysis of a cardiac subgroup; however, randomization was not stratified for this group and the distribution of known and unknown confounders may not be balanced. Although differences in cardiac biomarkers were reported in a post-hoc analysis between patisiran and placebo for the modified intention-to-treat population, no definitive conclusions regarding the effect of patisiran on cardiac disease progression can be made because of the methodological issues described in the clinical report.

In the extrapolation period, it was assumed that patients on BSC and inotersen would have an increase of NT-proBNP of 5,448 pg/mL every 18 months, whereas patients on patisiran would continue to have an increase of NT-proBNP of 1,311 pg/mL as observed in the APOLLO study.[8] The manufacturer used a study by Ruberg et al. (2012) to inform the cardiac progression of inotersen and BSC in the extrapolation period.[10] This study examined patients with the valine to isoleucine at position 122 (V122I) mutation (28%) and wild-type (62%) transthyretin amyloidosis. The V122Imutation is primarily cardiomyopathy related and only two patients in the APOLLO trial were reported to have this mutation type.[7,4] A clinical expert consulted by CADTH confirmed that patients with the V122I mutation would be expected to have more rapid cardiac disease progression relative to hATTR amyloidosis patients without the V122I mutation. Conversely, in the APOLLO trial, 43% of patients had the valine to methionine substitution at position 30 (V30M) mutation,[4] which is primarily associated with neuropathy.[7] Therefore, the study used to estimate NT-proBNP progression for patients on inotersen and BSC within the extrapolation period had patients with a greater risk of cardiac progression than that of all patient recruited in the APOLLO trial.

This assumption improves the life expectancy and quality of life of patients on patisiran compared with patients on inotersen or BSC.

6) **Uncertainty in the price of the comparator:** Although inotersen was approved in October 2018,[11] its public price in Canada was unavailable at the time of the review. Furthermore, the manufacturer applied monitoring costs that would be expected, given the product monograph for inotersen. However, the manufacturer of inotersen has released a statement saying that it is sponsoring a monitoring program to address the increased monitoring required for inotersen noted in the product monograph. Such monitoring programs have similarly been introduced in other international jurisdictions.[12,13]

7) **Long-term cost-effectiveness is uncertain:** Clinical data on patisiran were limited to a single 18-month randomized controlled trial.[8] Despite the availability of open-label extension studies, there remains uncertainty as to the long-term safety and efficacy of patisiran. Consultation with clinical experts noted that patisiran may be used in patients, even after progression to later stages of the condition. The clinical trial recruited patients with stage I or stage II polyneuropathy and New York Heart Association class I or class II heart failure and excluded those with advanced neuropathy or cardiac manifestations.[8] Although open-label extension studies are available,[14,15] these are limited in that they represent a select patient population as patients with poorer outcomes have a higher likelihood of withdrawing. Given that the treatment effects for patisiran informing the economic model are derived from a single clinical study, there is uncertainty as to the long-term response of patisiran beyond the observed trial period as a patient's disease progresses. In the manufacturer's economic model, treatment effects were assumed to persist beyond the observed period. Despite uncertainty to the appropriateness of this assumption, CADTH was unable to address this uncertainty.

Other limitations identified include the following:

8) **Adherence:** The manufacturer assumed that the adherence of patisiran would reflect the trial-reported relative dose intensity, which was calculated as the number of doses received in the APOLLO trial divided by the number of doses indicated (0.97).[8] The relative dose intensity lowered the acquisition cost of patisiran to 97%. However, patients were assumed to be fully compliant on inotersen. According to the clinical

experts consulted by CADTH on this review, patients are likely to remain on treatment, given the limited treatment options for this condition. Discontinuation would primarily be due to AEs in which inotersen was expected to have a more severe AE profile. The manufacturer's assumption lowers the cost of patisiran compared with inotersen and BSC.

9) **Drug administration cost:** Drug administration costs were overestimated for both patisiran and inotersen. The manufacturer's model assumed that, for each administration, the cost of IV infusion for patisiran would be $500. Previous CADTH reviews have used a cost of $121 per hour of infusion. The estimated infusion time of patisiran is 80 minutes,[1] suggesting an infusion cost of $161 per infusion. Furthermore, the manufacturer assumed that the administration of inotersen would be done in a clinic and applied $6.75 for each administration. Yet the product monograph for inotersen notes that the injection of inotersen is to be self-administered.[11]

CADTH Common Drug Review Reanalyses

Before undertaking any reanalyses, CADTH corrected programming to the manufacturer's probabilistic analysis (i.e., deterministic values were drawn for the efficacy inputs in the probabilistic analysis). CADTH subsequently conducted the following reanalyses to address the key limitations previously described.

1) A sequential analysis was undertaken. Different approaches were taken to calculate the efficacy and extrapolation transition matrices, depending on the comparator selected. To facilitate a sequential analysis, two changes were made to the model:
    a) Transition matrix during the efficacy period: The transition matrix for patisiran was informed directly by the available data from the APOLLO study and the estimated relative effect of inotersen was applied to the trial evidence of patisiran to derive the transition matrix for inotersen.
    b) Transition matrix during the extrapolation period: Transition matrices for BSC and patisiran were calculated in an identical manner.

The transition matrix for inotersen was calculated by using the trivariate transition outcomes (improve, remain stable, or progress) informed by the manufacturer's network meta-analysis and adjusting the patisiran shift table that detailed the number of patients moving from PND and NT-proBNP states at baseline and reaching other states after 18 months, as reported in the APOLLO trial (see Table 3). The manufacturer's approach for deriving transition probabilities for the shift tables was based on the Bayesian method proposed by Briggs et al.,[16] using a Dirichlet distribution with non-informative prior.

While the transition matrix in the efficacy period for BSC and patisiran were informed by the available data from the APOLLO study, the manufacturer's submitted model employed different assumptions to estimate the transition matrix in the extrapolation period. In the manufacturer's submitted model, to estimate transitions for patisiran in the extrapolation period, trial data was used to estimate transitions to adjacent health states; it was assumed, using a prior probability of 1/144, that patients could transition to non-adjacent states. To estimate transitions for BSC in the extrapolation period, trial data were used to estimate transitions to adjacent health states plus a transition to a health state two PND scores worse; it was assumed, using a prior probability of 1/144, that patients could transition to other non-adjacent states. Evidence from the APOLLO trial reports patients on patisiran worsening by more than one PND score; however, this was not included in the

manufacturer's calculations of the transition probabilities in the extrapolation period. Given the available data, the same methods for estimating the patisiran transition probabilities were used to estimate the BSC transition probabilities (see Table 16). Furthermore, a conservative approach was set in terms of the handling of missing PND data by assuming that patients with missing data reflected a worsened PND stage.

This revision meant that the costs and outcomes for patisiran did not change based on whether it was compared with BSC or inotersen. This also allowed the incremental cost-effectiveness ratio to be correctly calculated by appropriately considering dominated treatments.

Table 3: Shift Table (From Baseline to 18 Months), Patients in Inotersen, Adjusted Based on the Network Meta-Analysis

From/To		NT-proBNP < 3,000 pg/mL						NT-proBNP ≥ 3,000 pg/mL					
		0	I	II	IIIA	IIIB	IV	0	I	II	IIIA	IIIB	IV
NT-proBNP < 3,000 pg/mL	0	[redacted]											
	I		[redacted]										
	II			[redacted]									
	IIIA				[redacted]								
	IIIB					[redacted]							
	IV						[redacted]						
NT-proBNP ≥ 3,000 pg/mL	0							[redacted]					
	I								[redacted]				
	II									[redacted]			
	IIIA										[redacted]		
	IIIB											[redacted]	
	IV												[redacted]

NT-proBNP = N-terminal prohormone brain-type natriuretic peptide.

2) To correct for treatment-specific health state utilities and costs, CADTH assumed: a) no difference in utilities and, b) no reduction in health state costs between treatments.

3) The caregiver disutility was changed to zero in the CADTH reanalysis to more accurately reflect the model's perspective.

4) Given the difference in what is covered by UK and Canadian public payers, a number of costs were removed from the health state cost calculation. These costs included footcare, orthotics, dietician visits, laxatives, social welfare officer visits, dental care visits, acupuncture, occupational therapist visits, home service, special housing, and the Permobil ComfortRide mechanical wheelchair. In the CADTH base-case reanalysis, home renovation costs were further excluded with a scenario analysis that included home renovation costs, reported in Appendix 4.

5) The treatment effect of patisiran on cardiac outcomes was removed. The CADTH reanalysis assumed all treatments had a change in NT-proBNP equal to that observed in the placebo arm of the APOLLO trial for the full modelled time horizon.

6) The annual drug costs for inotersen were approximated to be $522,647 for the purpose of this review ($10,016.50 per syringe). This was based on adjusting the relative cost of patisiran and inotersen in the UK (details reported in Appendix 1).

7) Adherence for patisiran was assumed to be 100%.

8) The administration cost for inotersen was removed and infusion costs for patisiran were reduced to $161.

In addition, the following two changes were not considered key limitations but were updated.

9) **Discrepancies in baseline population characteristics: According** to the manufacturer, the demographics in the model (average age and percentage male) reflected the baseline characteristics of the APOLLO trial. However, the numbers used in the model were different than those reported in Table 12 of the clinical study report. The CADTH reference case used the baseline characteristics reported in the clinical review.

10) **Higher liver transplant costs:** The costs of liver transplant used in the manufacturer's model reflected the interprovincial billing rates for high-cost procedures and were higher than those used in previous CADTH reviews. The CADTH reference case used a lower liver transplant cost of $82,728.

Compared with the manufacturer's results, the CADTH sequential reanalysis estimated higher expected QALYs for BSC and inotersen, and a lower expected QALY for patisiran. Expected costs were lower for all comparators. In the CADTH reanalysis, the ICUR for patisiran was estimated to be $4,818,778 per additional QALY compared with BSC. Although the price of inotersen used in the analysis remains uncertain, at the CADTH assumed price of $10,016.50 per vial, inotersen was found to be extendedly dominated by patisiran (i.e., it was less effective and more costly than a combination of patisiran and BSC). Patisiran had a zero probability of being cost-effective at a $50,000 per QALY threshold (see Figure 1). In particular, the model was sensitive to the use of differential utilities and health state costs between treatments, the inclusion of the uncertain cardiovascular benefit, and the inclusion of health care resources not covered by Canadian public health care payers.

Table 4: CADTH Common Drug Review Reanalysis of Limitations

	Scenario	Treatment	QALYs	Cost ($)	(per QALY)
	Base Case, Submitted by Manufacturer (Compared With Inotersen)	Inotersen	2.85	6,396,601	
		Patisiran	6.60	6,073,125	Dominant
	Base Case, Submitted by Manufacturer (Compared With BSC)	BSC	0.78	1,243,769	
		Patisiran	7.14	5,935,174	$736,818
1	**Corrected Manufacturer's Base Case, Applying ITC Results to the Trial Analysis**	BSC	1.05	1,201,870	
		Patisiran	6.70	6,126,810	$871,426
		Inotersen	3.39	6,432,007	Dominated
1+2a	**Same Utilities for all Health States (i.e., No Difference Between Treatments)**	BSC	3.09	1,201,862	
		Patisiran	5.55	6,128,984	$2,008,447

	Scenario	Treatment	QALYs	Cost ($)	(per QALY)
		Inotersen	3.19	6,425,105	Dominated
1+2b	No Reduction in Health Care Resource Use Specific to Patisiran	BSC	1.03	1,206,234	
		Patisiran	6.70	6,385,154	$913,637
		Inotersen	3.42	6,426,874	Dominated
1+3	Excluding Caregiver Effects	BSC	1.55	1,199,902	
		Patisiran	6.91	6,118,370	$917,090
		Inotersen	3.87	6,403,495	Dominated
1+4	Removed Health Care Resource Use Costs Not Covered by Canadian Public Health Care Payers	BSC	1.05	431,413	
		Inotersen	3.41	5,679,648	Extendedly dominated
		Patisiran	6.70	5,875,392	$963,757
1+5	No Difference in NT-proBNP Progression Between Treatments	BSC	1.08	1,255,116	
		Patisiran	5.72	5,449,627	$904,095
		Inotersen	3.67	6,792,361	Dominated
1+6	Price of Inotersen: $40,066	BSC	1.03	1,204,286	
		Inotersen	3.40	5,833,389	Extendedly dominated
		Patisiran	6.70	6,111,726	$865,950
1+7	100% Adherence	BSC	1.04	1,207,494	
		Patisiran	6.71	6,298,979	$898,535
		Inotersen	3.41	6,431,837	Dominated
1+8	Corrected Administration Costs	BSC	1.03	1,212,373	
		Patisiran	6.72	6,065,485	$851,640
		Inotersen	3.41	6,434,559	Dominated
1+9	Population Characteristics From the Trial as Reported in Table 12 of the Clinical Study Report	BSC	1.08	1,080,667	
		Patisiran	6.23	5,687,389	$895,661
		Inotersen	3.16	5,884,821	Dominated
1+10	Updated Liver Transplant Cost	BSC	1.03	1,213,101	
		Patisiran	6.71	6,133,265	$867,553
		Inotersen	3.39	6,442,905	Dominated
CADTH Base Case (1+2a+2b+3+4+5+6+7+8+9+10)		BSC	3.65	371,029	
		Inotersen	3.69	4,953,048	Extendedly dominated
		Patisiran	4.62	5,059,913	$4,818,778

BSC = best supportive care; ITC = indirect treatment comparison; NT-proBNP = N-terminal prohormone brain-type natriuretic peptide; QALY = quality-adjusted life-year.

Two-way price reduction analysis was undertaken to determine what price patisiran would have to be in order to be considered cost-effective, while considering variability in the price of inotersen. At CADTH's assumed price of inotersen ($10,016.50 per syringe), a 98%

reduction in the price of patisiran is associated with a probabilistic ICUR of $43,333 per QALY compared with BSC (patisiran dominates inotersen).

Table 5: CADTH Common Drug Review Reanalysis of Price Reduction Scenarios

		Price of Inotersen (Based on CADTH Estimate)					
		No Reduction	**10% Reduction**	**30% Reduction**	**50% Reduction**	**70% Reduction**	**90% Reduction**
Price of Patisiran	**Submitted**	If λ < $4.8 M BSC If λ ≥ $4.8 M patisiran	If λ < $4.8 M BSC If λ ≥ $4.8 M patisiran	If λ < $4.8 M BSC If λ ≥ $4.8 M patisiran	If λ < $4.8 M BSC If λ ≥ $4.8 M patisiran	If λ < $4.8 M BSC If λ ≥ $4.8 M patisiran	If λ < $4.7 M BSC If λ ≥ $4.7 M patisiran
	10% Reduction	If λ < $4.3 M BSC If λ ≥ $4.3 M patisiran	If λ < $4.4 M BSC If λ ≥ $4.4 M patisiran	If λ < $4.3 M BSC If λ ≥ $4.3 M patisiran	If λ < $4.4 M BSC If λ ≥ $4.4 M patisiran	If λ < $4.3 M BSC If λ ≥ $4.3 M patisiran	If λ < $4.3 M BSC If λ ≥ $4.3 M patisiran
	30% Reduction	If λ < $3.4 M BSC If λ ≥ $3.4 M patisiran	If λ < $3.3 M BSC If λ ≥ $3.3 M patisiran	If λ < $3.4 M BSC If λ ≥ $3.4 M patisiran	If λ < $3.3 M BSC If λ ≥ $3.3 M patisiran	If λ < $3.3 M BSC If λ ≥ $3.3 M patisiran	If λ < $3.3 M BSC If λ ≥ $3.3 M patisiran
	50% Reduction	If λ < $2.4 M BSC If λ ≥ $2.4 M patisiran	If λ < $2.4 M BSC If λ ≥ $2.4 M patisiran	If λ < $2.4 M BSC If λ ≥ $2.4 M patisiran	If λ < $2.4 M BSC If λ ≥ $2.4 M patisiran	If λ < $2.4 M BSC If λ ≥ $2.4 M patisiran	If λ < $2.4 M BSC If λ ≥ $2.4 M patisiran
	70% Reduction	If λ < $1.4 M BSC If λ ≥ $1.4 M patisiran	If λ < $1.4 M BSC If λ ≥ $1.4 M patisiran	If λ < $1.4 M BSC If λ ≥ $1.4 M patisiran	If λ < $1.4 M BSC If λ ≥ $1.4 M patisiran	If λ < $1.4 M BSC If λ ≥ $1.4 M patisiran	If λ < $1.4 M BSC If λ ≥ $1.4 M patisiran
	90% Reduction	If λ < $430 K BSC If λ ≥ $430 K patisiran	If λ < $430 K BSC If λ ≥ $430 K patisiran	If λ < $430 K BSC If λ ≥ $430 K patisiran	If λ < $430 K BSC If λ ≥ $430 K patisiran	If λ < $430 K BSC If λ ≥ $430 K patisiran	If λ < $440 K BSC If λ ≥ $440 K patisiran

λ: willingness-to-pay threshold; BSC = best supportive care; K = thousand; M = million.

Issues for Consideration

- Tafamidis is available through the Health Canada Special Access Programme for patients with transthyretin amyloid cardiomyopathy.
- The administration of patisiran may require access to specialized infusion clinics. The manufacturer provided limited details on its distribution plans for this drug and concerns may arise over the accessibility of infusion clinics to administer this treatment.
- The role of liver transplant is unclear. According to the clinical experts consulted by CADTH, it could be plausible that patients with hATTR amyloidosis polyneuropathy who receive liver transplants may continue to use patisiran. The potential cost-effectiveness in this clinical population remains unclear, given that the existing trials have not studied this patient population.
- According to Health Canada, a patient support program is currently in development. Details regarding the program are not currently available.

Patient Input

The Canadian Organization for Rare Disorders (CORD) reported that hATTR amyloidosis is a debilitating condition that affects multiple systems in the body. It results in significant physical damage, pain, and psychological distress, and impacts daily functioning and quality of life. Patients experience symptoms of neuropathy, gastro paralysis, diarrhea, effects on the heart, deterioration of muscles with effects on mobility, and weight loss. CORD undertook a survey that found patients rated symptoms of nerve damage as the most difficult of symptoms, with one-third reporting these symptoms having serious impact and one-fifth reporting these symptoms to be incapacitating. The second most difficult symptom was gastrointestinal, with 51% reporting serious or incapacitating effects of gastrointestinal-related sexual dysfunction, sweating, dizziness upon standing, and weight loss. Other gastrointestinal symptoms, such as diarrhea, nausea, constipation, and urinary tract infection, were serious or incapacitating among one-third of respondents. Cardiac symptoms, such as palpitations, arrhythmia, and chest pain, were reported as serious or incapacitating by 40% of patients, but were not present or posed minor difficulty in 50% of patients. Other cardiac symptoms, such as leg swelling, fatigue, shortness of breath, and dizziness, were not present or minor in about 40% of respondents and serious in about 25%.

In the CORD survey, liver transplant was rated as very effective by the Canadian patients. Two patients reported that tafamidis was somewhat effective and one patient said it was not at all effective. Treatments for inflammation (i.e., diflunisal) were rated as moderately effective by about 50% of respondents. Among patients taking medications for cardiac management (e.g., blood pressure and arrhythmia), most reported that they worked well or very well. The most frequently reported treatment (64%) was diflunisal.

Conclusions

The key limitations of the manufacturer's analysis include the use of different estimates of efficacy for patisiran depending on the comparator(which made considering all comparators within one analysis problematic), uncertain and optimistic cardiovascular benefit assumed for patisiran, the application of using treatment-specific health state utilities, and the inclusions of health care resources not covered by Canadian public health care payers. CADTH found that the results were sensitive to the identified limitations. CADTH reanalysis estimated the ICUR for patisiran to be $4,818,778 per additional QALY compared with BSC. A price reduction of 98% would be required for the ICUR for patisiran to fall below the $50,000 per QALY threshold.

The economic findings require cautious interpretation, especially given the uncertainty in the true price of inotersen.

Appendix 1: Cost Comparison

The comparators presented in Table 6 have been deemed to be appropriate by clinical experts. Comparators may be recommended (appropriate) practice, versus actual practice. Comparators are not restricted to drugs, but may be devices or procedures. Costs are manufacturer list prices, unless otherwise specified. Existing product listing agreements are not reflected in the table and as such may not represent the actual costs to public drug plans.

Table 6: CADTH Common Drug Review Cost-Comparison Table for Drug Therapies for Adults With Hereditary Transthyretin-Mediated Amyloidosis With Polyneuropathy

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Dosage	Average Annual Drug Cost ($)
Patisiran (Onpattro)	2 mg/mL	IV	13,022.0226[a]	0.3 mg/kg IV infusion once every three weeks Max. dose: 30 mg	451,430 to 677,145[b]
Inotersen (Tegsedi)[c]	189 mg/mL	Pre-filled syringe	No public Canadian price available	284 mg SC once weekly	No publicly available Canadian price[d]

max. = maximum; SC = subcutaneous.

Note: All prices exclude dispensing fees.[17] First year is assumed to be 52 weeks long.

[a] Manufacturer-submitted price.[2]

[b] Assumes drug wastage. Patients between 34 kg and 66 kg of body weight require two vials per dose while those between 67 kg and 100 kg require three vials.

[c] Currently under review at CADTH.

[d] Annual drug costs for inotersen were approximated to be $522,647 for the purpose of this review, based on publicly available UK costs. Specifically, the annual cost of patisiran in Canada was adjusted by the relative ratio of the cost of patisiran (£399,176 annually,[18] assumed for a 67 kg patient, factoring drug wastage) and the cost of inotersen (£308,100 annually).[19]

Table 7: CADTH Common Drug Review Cost-Comparison Table for Products Available Through Health Canada's Special Access Programme for Adults With Hereditary Transthyretin-Mediated Amyloidosis With Polyneuropathy

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Dosage	Average Annual Drug Cost ($)
Tafamidis (Vyndaqel)	20 mg	Capsule	No public Canadian price available	20 mg orally once daily[a]	No publicly available Canadian price[b]

CDR = CADTH Common Drug Review.

[a] Dosage provided from the European public assessment report for tafamidis.[20]

[b] Annual drug costs for tafamidis were approximated to be $157,908 for the purpose of this review, based on publicly available German costs. Specifically, the annual cost of patisiran in Canada was adjusted by the relative ratio of the cost of patisiran (€362,500 annually,[21] assumed for a 67 kg patient, factoring drug wastage) and the cost of tafamidis (€84,534 annually).[19]

Table 8: CADTH Common Drug Review Cost-Comparison Table for Off-Label Drug Therapies for Adults with Hereditary Transthyretin-Mediated Amyloidosis With Polyneuropathy

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Dosage	Average Annual Drug Cost ($)
Diflunisal	250 mg	Tablet	0.2412[a]	250 mg twice daily[b]	176.08

[a] Price from BC PharmaCare Formulary (accessed March 1, 2019).[22]

[b] Recommended daily dosage from a clinical trial examining the effect of diflunisal on familial amyloidosis.[23] The appropriateness of this dosage was confirmed with CADTH clinical experts consulted for this review.

Appendix 2: Summary of Key Outcomes

Table 9: When Considering Only Costs, Outcomes & Quality of Life, how Attractive is Patisiran Relative to BSC for the Treatment of Polyneuropathy in Adult Patients With Hereditary Transthyretin-Mediated Amyloidosis?

	Attractive	Slightly Attractive	Equally Attractive	Slightly Unattractive	Unattractive	NA
Costs (total)					✓	
Drug treatment costs alone					✓	
Clinical outcomes	✓					
Quality of life	✓					
Incremental CE ratio (CDR reanalysis)	$ 4,818,778 per additional QALY					

BSC = best supportive care; CDR = CADTH Common Drug Review; CE = cost-effectiveness; NA = not applicable; QALY = quality-adjusted life-year.

Appendix 3: Additional Information

Table 10: Submission Quality

	Yes/ Good	Somewhat/ Average	No/ Poor
Are the methods and analysis clear and transparent?	✓		
Comments Reviewer to provide comments if checking "no"			
Was the material included (content) sufficient?			✓
Comments Reviewer to provide comments if checking "poor"	The manufacturer had errors in coding the probabilistic analyses in that deterministic values were drawn for the transition probabilities defined by the transition matrix and with certain cost inputs.		
Was the submission well organized and was information easy to locate?		✓	
Comments Reviewer to provide comments if checking "poor"			

Table 11: Authors Information

Authors of the Pharmacoeconomic Evaluation Submitted to CADTH Common Drug Review

☐ Adaptation of global model/Canadian model done by the manufacturer

☐ Adaptation of global model/Canadian model done by a private consultant contracted by the manufacturer

☐ Adaptation of global model/Canadian model done by an academic consultant contracted by the manufacturer

☒ Other (please specify): Uncertain as not indicated in the submission from the manufacturer

	Yes	No	Uncertain
Authors signed a letter indicating agreement with entire document			✓
Authors had independent control over the methods and right to publish analysis			✓

Appendix 4: Summary of Other Health Technology Assessment Reviews of Drug

Table 12: Other Health Technology Assessment Findings

	(NICE) 2018[18]
Treatment	Patisiran: 0.3 mg/kg infusion every three weeks
Price	Patisiran: £7,676.47 per 10 mg/5 mL vial (C$13,279.53 based on the exchange rate from the Bank of Canada website)[24]
Similarities with CDR submission	• Similar Markov model structure developed based on PND scores and NT-proBNP levels, with cut-off of ≥ 3,000 pg/mL to indicate greater cardiac involvement • 6-month cycle, lifetime time horizon • All patients, apart from those in PND 0, eligible for treatment • Increased mortality risk for patients in more severe NT-proBNP category • Disease transitions derived from APOLLO trial • Used non-informative priors to inform transition probabilities between all alive health states. Approach meant patients, regardless of treatment, can move to an improved health state in the first 18 months. The transition matrix in the efficacy period (in the first 18 months) for BSC was also used in the extrapolation period (> first 18 months) • Used Delphi approach to elicit expert opinion on resource use • A regression equation derived from APOLLO was used to determine utilities at all modelled time points. Covariates in regression included PND state, treatment, time, and interaction factor between treatment and time. For patisiran patients, utility increases over time to a maximum cap. For patients receiving BSC, utility decreases over time, to a minimum limit • Frequencies of adverse events from APOLLO[8]
Differences with CDR submission	• Comparator was BSC • Model structure: Liver transplant health states not included • Differential discount rate applied: 3.5% for costs, 1.5% for outcomes • Mortality risk increases with advancing PND score • Caregiver disutility of 0.01 applied to all patients in PND IV (disutility of 0.125 applied in manufacturer's CDR submission)
Manufacturer's results	In the probabilistic base case, the ICUR for patisiran compared with BSC was more than £100,000 per QALY gained. The incremental QALY gain for patisiran was 8.11 compared with BSC (ICUR confidential).
Issues noted by the review group	• PND score does not adequately capture the full condition as it only captures mobility impairment; FAP staging would incorporate autonomic symptoms. Consequently, the committee felt that since all aspects of the condition were not captured in the model, it may not reflect true cost-effectiveness. • Cycle length of 6 months is different than that of trial follow-up period of 18 months, resulting in challenges in calculating transitions. ERG-noted observed trial data (separated into 0 months to 9 months and 9 months to 18 months) could have been used; insufficient justification provided for the 6-month cycle length. • Differential discount rates (1.5% for outcomes and 3.5% for costs) are considered inappropriate as NICE reference case. In ERG-preferred analysis, a 3.5% discount rate was applied to both costs and outcomes. • Initial distribution of patients had 1 patient starting in FAP stage III, which was considered inappropriate as this was outside the product's marketing authorization. • HRQoL regression was unreliable; it omitted relevant covariates and the application of ceiling effects resulted in unrealistic utilities. • A single transition matrix was applied such that there was a constant treatment effect, even though the number of people discontinuing treatment was increasing. • Use of gamma function for estimating NT-proBNP transitions led all surviving BSC patients to develop NT-proBNP greater than 3,000 pg/mL after approximately 5 years. • There was uncertainty in the data source and the approach used to estimate mortality risk by PND group. • A mortality effect from cardiac involvement was included for low NT-proBNP states.

	(NICE) 2018[18]
Results of reanalyses by the review group	Results of the review group's reanalyses found a deterministic QALY gain of 6.85 for patisiran compared with BSC. The expected costs of BSC was £644,916 (patisiran's expected costs and ICER remained confidential).
Recommendation	Non-final decision (second meeting, February 2019): • patisiran not recommended for treatment of adults with hereditary transthyretin-mediated amyloidosis.[25] • recommendation based on lack of evidence on long-term benefits, uncertainty in economic modelling, and estimates of cost-effectiveness higher than considered acceptable for highly specialized technologies.[25]

BSC = best supportive care; C = Canadian; CDR = CADTH Common Drug Review; ERG = evidence review group; FAP = familial amyloidotic polyneuropathy; HRQoL = health-related quality of life; ICER = incremental cost-effectiveness ratio; ICUR = incremental cost-utility ratio; NICE = National Institute for Health and Care Excellence; NT-proBNP = N-terminal prohormone brain-type natriuretic peptide; PND = polyneuropathy disability; QALY = quality-adjusted life-year.

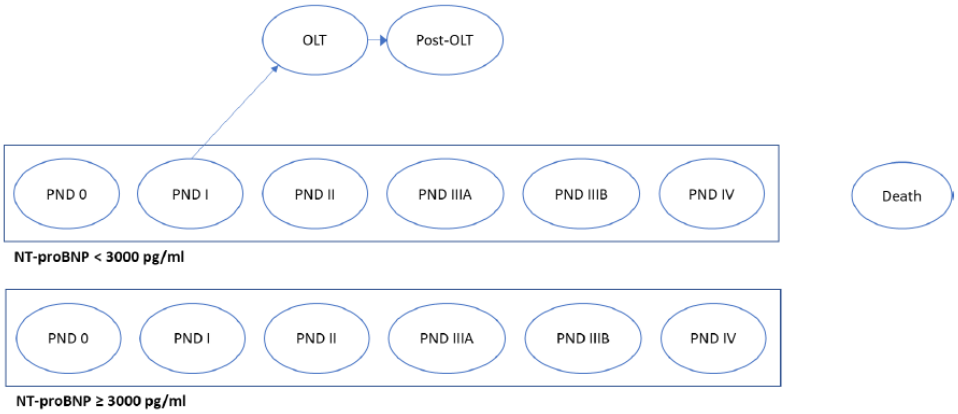
Appendix 5: Reviewer Worksheets

Manufacturer's Model Structure

The manufacturer submitted a Markov model to assess the cost-effectiveness of patisiran relative to inotersen in the treatment of polyneuropathy in adult patients with hereditary transthyretin-mediated amyloidosis under the base case. A scenario analysis was further conducted in which the comparator was best supportive care. Fourteen living health states measuring hereditary transthyretin-mediated amyloidosis disease progression were developed by combining polyneuropathy and cardiac outcomes, along with the possibility of receiving an orthotopic liver transplant (OLT). Polyneuropathy disability (PND) scores, a functional scale that measures ambulatory ability, were used to characterize polyneuropathy progression. The cardiac biomarker N-terminal prohormone brain-type natriuretic peptide (NT-proBNP) was used as an indicator of cardiac involvement, with PND health states stratified by NT-proBNP levels under 3,000 pg/mL or NT-proBNP levels equal to or greater than 3,000 pg/mL (which would be associated with poorer survival). A small proportion of patients may transition to the OLT health state and discontinue their drug regimen, based on transplant waiting list durations, where they remain for one cycle before transitioning to the post-OLT health state, simulating the clinical progression of the condition post-transplant. Figure 1 provides a graphical representation of the model structure.

Patients enter the model distributed across the NT-proBNP and PND I to PND III health states, according to APOLLO trial baseline distributions. Since patisiran is not indicated for asymptomatic patients, no patients start in the PND 0 states. In the manufacturer's submitted model, patients enter the model at an initial age of 58.8 years and are 70.5% male. In each six-month cycle, patients may remain in the same health state, or transition to a less or more severe health state. For instance, patients in PND I who improve may transition to PND 0 and those who regress may transition to PND II. In the manufacturer's base case, patients may only improve or regress to the PND health state adjacent to their current state whereas, in the manufacturer's scenario analysis that compared patisiran to best supportive care, patient-level data from the APOLLO trial informed the health state transitions and patients could improve or regress to any PND health state.

Figure 1: Model Structure[2]



NT-proBNP = N-terminal prohormone brain-type natriuretic peptide; OLT = orthotopic liver transplant; PND = polyneuropathy disability.

Source: Manufacturer's pharmacoeconomic submission.[2]

Table 13: Initial Distribution of Patient Cohort, by PND Score and NT-proBNP Levels, Used in Manufacturer's Submission[2]

PND State	% of Patients Starting in PND Health States (Initial NT-proBNP < 3,000 pg/mL)	% of Patients Starting in PND Health States (Initial NT-proBNP ≥ 3,000 pg/mL)	Total
PND 0	[redacted]	[redacted]	[redacted]
PND I	[redacted]	[redacted]	[redacted]
PND II	[redacted]	[redacted]	[redacted]
PND IIIA	[redacted]	[redacted]	[redacted]
PND IIIB	[redacted]	[redacted]	[redacted]
PND IV	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	

NT-proBNP = N-terminal prohormone brain-type natriuretic peptide; PND = polyneuropathy disability.

Table 14: Data Sources

Data Input	Description of Data Source	Comment
Baseline characteristics	The following baseline characteristics were defined in the manufacturer's model and were informed by the APOLLO trial:[8] • proportion of males — 70.5% • patient initial age — 58.8 years (95% CI, 57.3 to 60.4) Distribution of patient weight: • 35 kg to 66 kg: [redacted]% • 67 kg to 99 kg: [redacted]% • 100 kg to 132 kg: [redacted]% Distribution of model cohort at baseline by PND score and NT-proBNP levels are presented in Table 13.	Minor discrepancies noted. According to the APOLLO CSR, the following were the baseline characteristics at screening in the mITT population:[8] • proportion males — 74.2% • patient initial age — 60.5 years (SD: 11.61) Appropriate. Clinical expert confirmed that the distribution of patients' weight recruited in the APOLLO trial would be generalizable to a Canadian setting. Unclear. CADTH reviewers noted that this distribution differed from that provided in the APOLLO trial CSR.[8] The initial distribution of patients in the APOLLO trial mITT population are reported in the clinical review. CADTH reviewers were unable to validate how the manufacturer determined the initial distribution of patients by PND score and NT-proBNP. As there is little known about patients with hATTR in Canada, it is difficult to assess the external validity of the APOLLO trial baseline characteristics. Also, given the rare nature of the disease, the clinical experts consulted by CADTH for this review were unable to confirm whether trial data were reflective of the Canadian population.
Efficacy	Transition matrix reflected movement between PND and NT-proBNP health states. Different transition matrices were derived for the efficacy and extrapolation period, reflecting the trial length of APOLLO. *Efficacy period (≤ 18 months)* Transition probabilities for patisiran and BSC were derived from the APOLLO trial.	Using the APOLLO trial data, the Bayesian method was applied (Dirichlet distribution with a non-informative prior). No correction was made to missing data.

Data Input	Description of Data Source	Comment
	ITC was used to estimate the relative efficacy of patisiran and inotersen [redacted]	Transition matrices were derived as trivariate outcomes: improve, remain stable, or progress (with progression or improvement only possible between adjacent health states). Relative treatment effects, in terms of relative risk of response to treatment (defined as "improve" or "remain stable"), were derived by MAIC without justification in their base-case analysis. The manufacturer evaluated the Bucher analysis results in a scenario analysis. The CADTH clinical review team found that the MAIC analysis with imputation was the most appropriate ITC analysis, but noted several limitations with the approach: • MAIC breaks randomization, and while MAIC adjusts for differences in observed baseline characteristics between the trials, unobserved potential confounders that would have been balanced in randomization may have an effect on the outcome • imputation was important because of different rates of dropouts in trial arms and across trials • APOLLO study results were extrapolated using a linear regression model without reporting the details and diagnostics of the model, adding uncertainty in the results of the ITC • wide CIs were noted in the binary outcomes, indicating low statistical power and suggesting increased uncertainty in the results • there was no comparison with tafamidis.
	Mean changes in NT-proBNP were derived from the APOLLO trial in which the treatment arm informed patisiran's value (Δ104 pg/mL) while the placebo arm informed inotersen's and BSC's value (Δ1,311 pg/mL).	Inappropriate. Although the mean change from baseline to month 18 in the mITT population does differ, the CADTH clinical review team noted several concerns with the cardiac data, concluding that no conclusions can be drawn with regard to NT-proBNP data reported in APOLLO: • the APOLLO trial was not designed to assess mortality or cardiac morbidity and there was no pre-planned statistical testing of the cardiac biomarker and echocardiogram data for the mITT population • it was unclear whether the cardiac biomarkers measured represent direct clinical benefit • there was a difference in the proportion of patients with a history of cardiac disorders between groups at baseline.
	Extrapolation period (> 18 months) Transition probabilities were derived based on change in NT-proBNP.	Missing data were excluded when determining transition probabilities for BSC in the extrapolation period. During the extrapolation period, the BSC sample size is 55 while the sample size for the efficacy period is 77.
	Mean change was assumed to remain constant to the change observed in the efficacy period for patisiran. For inotersen	Inappropriate. The study by Ruberg et al. (2012) examined patients with the V122I mutation (28%) and wild-type TTR (62%). The V122I mutation is primarily cardiomyopathy related and only 2 patients in

Data Input	Description of Data Source	Comment
	and BSC, the change in NT-proBNP was informed by an observation study.[10]	APOLLO had this mutation type.[7,4] A clinical expert consulted by CADTH confirmed that patients with V122I mutation would be expected to have more rapid cardiac disease progression relative to hATTR patients without the V122I mutation. In APOLLO, 43% of patients had the V30M mutation,[4] which is primarily associated with neuropathy.[7] The study used to estimate NT-proBNP progression in BSC and inotersen reflected a population with greater risk of cardiac progression than that of APOLLO.
	OLT: Manufacturer assumed that 2.5% of patients in the PND I with NT-proBNP < 3,000 mg/mL health state during the third model cycle may receive OLT.	Uncertain. Scenario analyses were conducted to better understand the structural uncertainty of including this set of health states.
	PND progression post OLT: 29.6% of patients progress after 34.8 months.[26]	The clinical expert consulted by CADTH for this review noted that the proportion of patients receiving liver transplant would be low (less than 10%) and would most likely be in patients with PND stage I, and that the assumptions on the disease progression post OLT are likely appropriate.
Natural history	Progression of polyneuropathy described by PND score.	Inappropriate.[27,28] PND is a functional scale that measures ambulatory ability. As noted in the clinical review, there are several limitations with the use of PND scores: • PND scores only reflect mobility impairment • PND scores do not capture symptoms associated with autonomic dysfunction • PND scores might not be sensitive to changes over the short period of the trial • the classification of patients by PND score is subjective and patients may fall within the grey zones between stages. Additionally, there is potential for overlap in PND scores.
	Cardiac involvement described by the cardiac biomarker NT-proBNP that was stratified by NT-proBNP of less than or greater than or equal to 3,000 pg/mL.	Uncertain. NT-proBNP is correlated with some cardiac morbidity markers in patients with hATTR, including septal thickness, left ventricular posterior wall thickness, and left atrial diameter.[29] However, the appropriateness of using a cut-off of 3,000 pg/mL as an indicator of cardiac involvement is uncertain in hATTR patients. While the study by Gillmore et al. (2017) explored the use of 3,000 pg/mL as a staging system for cardiac transthyretin patients, the study population included both wild-type and hATTR patients. Additionally, a number of studies in mixed amyloidosis patient populations (i.e., some studies may have included wild-type or light-chain amyloidosis patients) have explored a variety of NT-proBNP thresholds as predictive of survival or cardiac involvement. [30-35] The appropriateness of using the 3,000 pg/mL threshold is therefore uncertain in hATTR patients.
Utilities	Utilities were derived from EQ-5D data collected across all time points in the APOLLO study using a Canadian value	Inappropriate. Treatment-specific utility values were utilized such that, when remaining in the same health state, the utility of patients receiving patisiran

Data Input	Description of Data Source	Comment
	set. Health state utilities were estimated from a regression analysis of EQ-5D with the following covariates: health state (PND), treatment, time, and interaction term between treatment and time. Utility estimates were constrained to not exceed age- and gender-matched utility estimates of a general Canadian population.	improved while the utility of those receiving placebo worsened. Based on the *Guidelines for the Economic Evaluation of Health Technologies: Canada*, treatment-specific utility values are not considered to be an appropriate approach for the base case.[5] The regression-based approach further led to results such as the utility for PND I (0.7405) being higher than that for PND 0 (0.7403), despite being a more severe health state. This suggests that the health states used in the model do not appropriately capture the important changes in health and underlying disease progression.
	Inotersen utilities were adjusted. For the same health state, [redacted] This was based on the mean difference in Norfolk Quality of Life-Diabetic Neuropathy questionnaire scores for patisiran compared with inotersen (−11.3; 95% CI, −19.8 to −2.9) from the manufacturer's submitted ITC. This was converted into an EQ-5D disutility using a mapping algorithm from THAOS registry data.	As previously noted, CADTH does not consider treatment-specific utilities to be appropriate in the base case.[5]
	Disutility was applied for NT-proBNP greater than 3,000 pg/mL: 0.0635.[36]	Uncertain. The manufacturer applied the utility weight associated with heart failure. Karabulut et al. (2005) studied the association between NT-proBNP levels and heart failure and noted that New York Heart Association class III and class IV were associated with a mean NT-proBNP of 2,111 pg/mL and 6,471 pg/mL, respectively.[39]
	Carer disutility was applied to all patients in PND IV, based on a NICE appraisal on treatments for multiple sclerosis.[37]	Inappropriate. Carer disutility is more appropriate in an analysis examining a societal perspective.[5]
	One-time disutility was applied when liver transplant occurs.[38]	Uncertain but unlikely to impact the results. Although the study was conducted in a UK setting and was not specific to hATTR patients receiving transplant, the proportion of patients receiving OLT is low.
	In patients who do not progress post OLT, the maximum utility estimate reported in APOLLO was applied (0.950) while in patients who progress post OLT, the average utility estimate from the APOLLO trial was applied.	Inappropriate. According to the clinical expert consulted by CADTH for this review, patients receiving liver transplants will require ongoing follow-up and lifelong treatment with antirejection medications, influencing their post-transplant quality of life.
	The effect of AEs on HRQoL was not considered.	Inappropriate. The manufacturer claimed that utilities associated with AEs were not included to avoid double counting since treatment-specific utilities were already used. However, the application of treatment-specific utilities is inappropriate. Disutility from AEs should be explicitly modelled.
AEs	Only serious AEs with greater than 2% occurrence in each treatment arm of the APOLLO study were considered in the	Inappropriate, although conservative, as the approach favoured inotersen. According to the clinical experts consulted by CADTH, rates of AEs are

Data Input	Description of Data Source	Comment
	model. AEs for patisiran and BSC were sourced from the APOLLO trial. For inotersen, only severe AEs that were also recorded during the APOLLO trial were included. Rates of AEs for inotersen were sourced from the NEURO-TTR trial.	expected to be higher with inotersen than patisiran, although this was not captured in the approach taken to model AEs.
Mortality	The mortality of patients with NT-proBNP < 3,000 pg/mL was calculated by applying a calibrated HR of death of 4.87 for hATTR to general Canadian population mortality risk (sourced from Statistics Canada life tables for 2014 to 2016).[40] The calibration target sets mean survival in untreated patients to 9.75 years.	Appropriate according to the clinical expert consulted by CADTH and the literature on hATTR patient survival.[42]
	Patients with NT-proBNP ≥ 3,000 pg/mL were associated with an additional mortality risk (HR = 1/0.508) over the mortality of patients with NT-proBNP < 3,000 pg/mL, based on a study that examined the association between mortality and NT-proBNP in TTR amyloidosis.[29]	Uncertain. According to clinical experts consulted by CADTH for this review, they would expect higher mortality as a function of cardiac disease progression. However, the appropriateness of the sources used in the manufacturer's model is uncertain. The manufacturer did not provide justification for how the study was selected. Specifically, this study — Kristen et al. (2017) —was based on the THAOS registry and had a median follow-up of 1.2 years. Additionally, wild-type patients were included and, as the clinical experts consulted for this review noted, a more rapid cardiac disease progression would be expected in hATTR patients relative to wild-type TTR.
	No excess mortality was considered as a function of PND score.	Appropriate. According to the clinical experts consulted by CADTH for this review, polyneuropathy itself is unlikely to be a primary cause of mortality in these patients.
	Survival post OLT estimated using survival data from Ericzon et al. (2015), with a Weibull function used to obtain probability of death at each cycle post-OLT health state.[41]	Appropriate. This study examined liver transplant in a 20-year retrospective analysis from the Familial Amyloidotic Polyneuropathy World Transplant Registry.
Resource Use and Costs		
Drug	**hATTR treatments** • Price of patisiran from the manufacturer[2] with premedication total cost of $7.24 per administration assumed • Price of inotersen estimated to be $45,130.70 per 4-syringe pack based on the maximum international reference price, converted to Canadian dollars	Appropriate Uncertain. There were no publicly available Canadian drug prices for inotersen at the time of this review. Using the maximum international reference drug price for inotersen may have overestimated its cost, favouring patisiran. CADTH revised the estimate of the price of inotersen based on an annual treatment cost of $522,647.
	Inotersen monitoring cost was $62.06 every 6 months. Source of costs: Ontario *Schedule of Benefits for Laboratory Services*.[43] • L393: CBC (platelet) $3.98	Inappropriate. The frequency of laboratory testing (6 months) is not consistent with the inotersen product monograph. Despite the discrepancy in the frequency of laboratory test monitoring, the expected difference in cost is likely to be small and unlikely to influence

Data Input	Description of Data Source	Comment
	• L191: alkaline phosphatase $1.28 • L068: creatinine clearance $1.03 • L067: creatinine not with L068	model results. Additionally, in some international jurisdictions, inotersen monitoring costs may be partly covered as part of an inotersen monitoring program (Akcea Connect).[13]
Administration	Patisiran: $500 per infusion session based on manufacturer's assumption. Inotersen: $6.75 per subcutaneous injection (Ontario's *Schedule of Benefits: Physician Services Under the Health Insurance Act*, code G373).[44]	Inappropriate assumption. Infusion costs were estimated based on a previous CADTH review for Lemtrada (2015)[45] and the expected duration of infusion (80 minutes). The resulting inflated infusion cost was $161. Inappropriate. As per inotersen's product monograph, inotersen is intended to be administered by the patient.[11]
Event	**Cost of liver transplant** • Transplant procedure: $118,348. Source: Interprovincial billing rates for high-cost procedures. • Follow-up transplant costs (every 6 months): $61.25. Source: Ontario's *Schedule of Benefits: Physician Services Under the Health Insurance Act*, code A134 (medical specific re-assessment). • Additional per cycle cost after PND progression: $31,049.40. Source: Assumed as the difference between the average cost in PND II to PND IV and the cost in PND I. **Costs of end-of-life care:** Adjusted cost based on the proportion of patients treated in hospital or hospice setting, the duration of stay, and cost per day. • Proportion of patients treated in hospital: 64.9%. Source: HQO palliative care patient deaths in hospitals, 2014 to 2015. • Number of days in hospital at end of life: 11.8. Source: OCCI code Z515. • Proportion of patients treated in hospice: 23.5%. Source: HQO palliative care patient deaths in hospitals, 2014 to 2015. • Number of days in hospice at end of life: 19.0. Source: Residential hospice working group environmental scan, 2015. • Community palliative care costs, per day: $126.00. Source: Home Care Ontario, Facts & Figures.	Inappropriate. The average total cost per case from the OCCI code 270 for liver, pancreas and duodenal transplant is $79,776 for 2016 to 2017 ($82,728, inflated 2019 value using Bank of Canada inflation calculator).[46,47] Unable to ascertain the accuracy of the cost estimates of end-of-life care. However, these are unlikely to have an impact on model results.
AEs	AE unit costs from the OCCI database[46]	Appropriate. All AEs were assumed to be treated in an inpatient setting. Given that only severe AEs were considered in the model, this approach to estimate AE costs is likely appropriate.
Health state	Per cycle costs for polyneuropathy and for cardiomyopathy and one-off costs for	Inappropriate and resulted in inflated costs. The Delphi panel reflected care approaches in the UK.[2]

Data Input	Description of Data Source	Comment
	entering a new PND stage were estimated by a Delphi panel of 7 European physicians experienced in treating hATTR patients in the UK.[2]	The clinical experts consulted by CADTH for this review commented that the clinical management of patients may be different in Canada compared with the UK. Additionally, some costs reflected personal and social services that are not considered appropriate for inclusion under a Canadian public health care payer perspective.[5] The experts also noted that physicians rarely categorize hATTR patients by disease stage. This may increase the difficulty for physicians in accurately estimating costs associated with states they rarely categorize patients by.
	Further assumed that patisiran would be associated with a reduction of health care resource utilization. Source: Delphi panel.	Likely resulted in double counting. According to the clinical experts consulted by CADTH for this review, patients in the same health state but receiving different treatments may consume fewer health care resources due to differences in AEs and drug administration that are already captured.

Δ = change; AE = adverse event; BSC = best supportive care; CI = confidence interval; CSR = clinical study report; EQ-5D = EuroQol five dimensions heath status questionnaire; hATTR = hereditary transthyretin-mediated amyloidosis; HR = hazard ratio; HQO = Health Quality Ontario; HRQoL = health-related quality of life; ITC = indirect treatment comparison; MAIC = matching-adjusted indirect comparison; mITT = modified intention-to-treat; NICE = National Institute for Health and Care Excellence; NT-proBNP = N-terminal prohormone brain-type natriuretic peptide; OCCI = Ontario Case Costing Initiative; OLT = orthotopic liver transplant; PND = polyneuropathy disability; po = per os, by mouth; SD = standard deviation; THAOS = Transthyretin Amyloidosis Outcomes Survey; TTR = transthyretin; V122I = valine to isoleucine substitution at position 122; V30M = valine to methionine substitution at position 30.

Table 15: Manufacturer's Key Assumptions

Assumption	Comment
PND scores were used to define health states associated with polyneuropathy.	PND scores only reflect mobility impairment and do not capture autonomic dysfunction symptoms. As identified by the manufacturer, the model structure does not account for changes in health-related quality of life from autonomic symptoms. Additionally, PND scores might not be sensitive to changes over the short trial period. Not capturing all disease effects in the model structure is inappropriate.
Patients were stratified into low or high cardiac involvement by NT-proBNP score (greater than or equal to 3,000 pg/mL for high cardiac involvement).	Uncertain. NT-proBNP has been found to be moderately correlated with left atrial diameter and strongly correlated with septal thickness and left ventricular wall thickness.[29] However, according to the clinical review, a variety of NT-proBNP thresholds have been explored in the literature as predictive of survival and cardiac involvement, and these studies have been conducted in mixed amyloidosis patient populations (i.e., some studies may have included wild-type transthyretin or light-chain amyloidosis patients).[30 31 32 33 34,35] Therefore, the appropriateness of the 3,000 pg/mL threshold as an indicator of cardiac involvement is uncertain in hATTR patients.
Patients remain on treatment for the duration of their lives.	Potentially appropriate. According to the clinical experts consulted for this review, the application of stopping rules is challenging, given the lack of other available treatment. Clinical experts noted that patients with end-stage cardiac disease or those with limited life expectancy would be considered unsuitable for treatment.
Patients may only improve or worsen to the health states adjacent to their current state.	Inappropriate. This approach relied on categorizing PND into a binary outcome and, as per the clinical review, leads to greater inaccuracies (wider confidence intervals).
Changes in NT-proBNP levels are assumed to be equal to that of placebo for patients receiving inotersen.	Appropriate given there is limited clinical data on the effects of inotersen on cardiovascular outcome.

Assumption	Comment
The efficacy of patisiran differed by the comparator.	Inappropriate. If the baseline patient population remains identical in the base case and scenario analysis comparing patisiran with BSC, the efficacy of patisiran should be identical.
Patients receiving patisiran may continue to improve in the extrapolation period.	Uncertain, but according to the clinical expert consulted in this review, this might be a fair assumption given the lack of long-term data.
Liver transplants are only possible in cycle iii of the model.	Inappropriate but unlikely to impact model findings. While the disease stage at which patients would be eligible for liver transplants (PND I) was validated as potentially appropriate with the clinical experts consulted by CADTH, it does not appear appropriate that the entire cohort of patients is only eligible for liver transplant for 1 cycle.
Price of inotersen.	Inappropriate. The manufacturer used the maximum international reference allowed by Canada's Patented Medicine Prices Review Board in estimating inotersen costs. Using the maximum inotersen price estimate is likely to favour patisiran.
The drug acquisition cost estimate for patisiran assumed drug waste.	Appropriate.

BSC = best supportive care; hATTR = hereditary transthyretin-mediated amyloidosis; NT-proBNP = N-terminal prohormone brain-type natriuretic peptide; PND = polyneuropathy disability.

Manufacturer's Results

In the manufacturer's base case, relative to inotersen, patisiran is associated with an additional quality-adjusted life-year (QALY) gain of 3.76 at an incremental cost of −$323,476. Patisiran was dominant over inotersen (patisiran was less costly and more effective). Relative to best supportive care, patisiran was associated with an incremental QALY gain of 6.37 at an incremental cost of $4,691,405, producing an incremental cost-utility ratio of $736,818 per QALY gained.

CADTH Common Drug Review Reanalyses

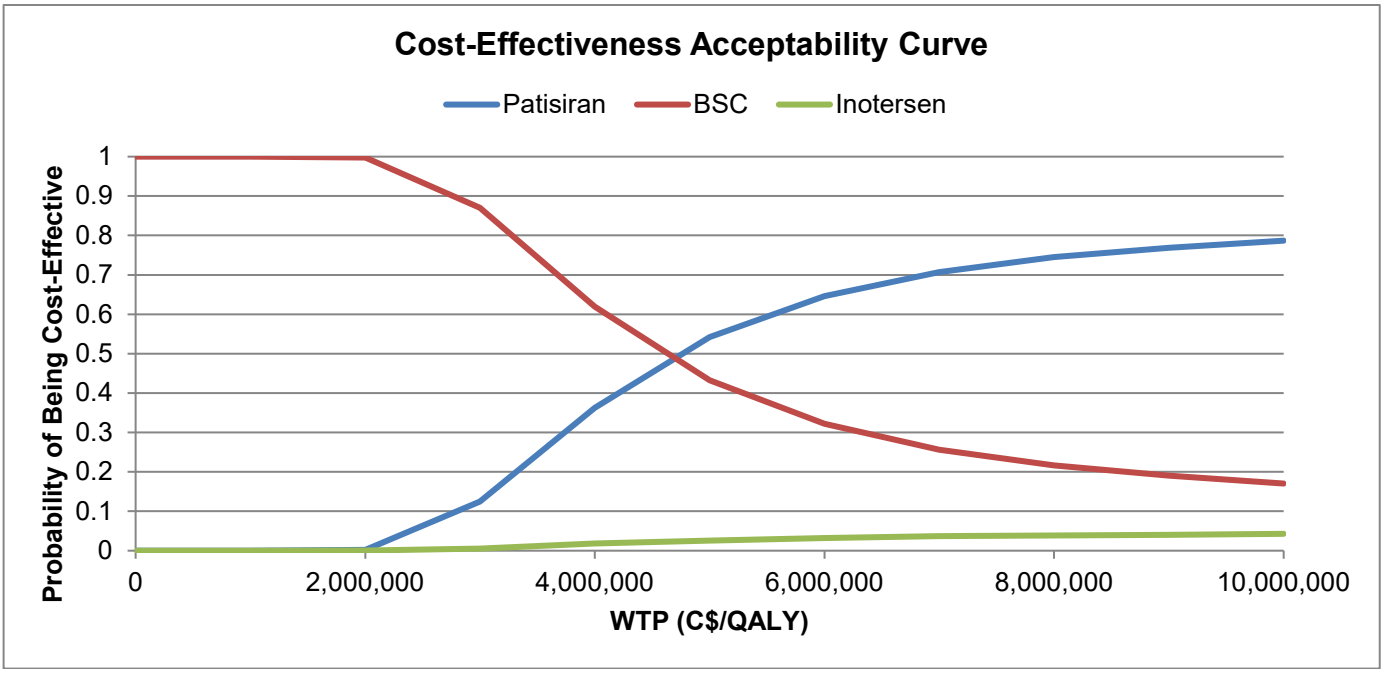
Table 16: Shift Table (Extrapolation Period), Patients on Best Supportive Care

From/To		NT-proBNP < 3,000 pg/mL						NT-proBNP ≥ 3,000 pg/mL					
		0	I	II	IIIA	IIIB	IV	0	I	II	IIIA	IIIB	IV
NT-proBNP < 3,000 pg/mL	0	[redacted]											
	I		[redacted]										
	II			[redacted]									
	IIIA				[redacted]								
	IIIB					[redacted]							
	IV						[redacted]						
NT-proBNP ≥ 3,000 pg/mL	0							[redacted]					
	I								[redacted]				
	II									[redacted]			
	IIIA										[redacted]		
	IIIB											[redacted]	
	IV												[redacted]

NT-proBNP = N-terminal prohormone brain-type natriuretic peptide.

A cost-effectiveness acceptability curve was estimated for the CADTH reanalysis. Figure 2 demonstrates that patisiran has a 0.00 probability of being cost-effective at willingness-to-pay thresholds of less than $2 million per QALY and was most likely to be a cost-effective intervention only at willingness-to-pay thresholds of more than $5 million per QALY.

Figure 2: Cost-Effectiveness Acceptability Curve



BSC = best supportive care; QALY = quality-adjusted life-year; WTP = willingness to pay.

The CADTH reanalysis was robust in the additional scenario analyses conducted to examine the exclusion of inotersen monitoring costs, the exclusion of liver transplants from the model, a stopping rule for patients progressing to PND IV, and decreases in the cost of inotersen of up to 50%. The CADTH reanalysis was also tested for different starting populations; results were relatively robust.

Table 17: CADTH Common Drug Review Scenario Analyses

	Scenario	Treatments	QALYs	Cost	(per QALY)
A	**CADTH Base Case and No Inotersen Monitoring Costs**	BSC	3.65	370,810	
		Inotersen	3.68	4,938,304	ED
		Patisiran	4.62	5,052,490	4,823,015
B	**CADTH Base Case and No Liver Transplant**	BSC	3.62	372,868	
		Inotersen	3.67	4,969,518	ED
		Patisiran	4.59	5,082,166	4,838,749
C	**CADTH Base Case and No Patients Receive Treatment in PND Stage IV**	BSC	3.63	371,573	
		Inotersen	3.68	2,971,942	ED
		Patisiran	4.61	4,394,145	4,109,883
D	**CADTH Base Case and all Patients Start in PND I With NT-proBNP < 3,000 pg/mL**	BSC	3.66	371,303	
		Inotersen	3.69	4,953,184	ED
		Patisiran	4.63	5,065,831	4,839,910
E	**CADTH Base Case and all Patients Start in PND I With NT-proBNP ≥ 3,000 pg/mL**	BSC	3.40	389,439	
		Inotersen	3.44	4,715,102	ED

	Scenario	Treatments	QALYs	Cost	(per QALY)
		Patisiran	4.30	4,816,093	4,896,114
F	**CADTH Base Case and all Patients Start With NT-proBNP ≥ 3,000 pg/mL**	BSC	3.37	390,341	
		Inotersen	3.42	4,702,899	ED
		Patisiran	4.28	4,801,422	4,864,006
G	**CADTH Base Case and Price of Inotersen is $32,053**	BSC	3.64	371,191	
		Inotersen	3.67	4,025,749	ED
		Patisiran	4.61	5,048,565	4,835,884
H	**CADTH Base Case and Price of Inotersen is $20,033**	BSC	3.65	370,223	
		Inotersen	3.69	2,650,265	ED
		Patisiran	4.61	5,049,747	4,854,249
I	**CADTH Base Case and Reported Cardiac Effects for Patisiran in the Trial Period Only**	BSC	3.63	372,930	
		Inotersen	3.68	4,950,969	ED
		Patisiran	4.61	5,058,316	4,788,898

BSC = best supportive care; ED = extended dominance; NT-proBNP = N-terminal prohormone brain-type natriuretic peptide; PND = polyneuropathy disability; QALY = quality-adjusted life-year.

References

1. Onpattro (patisiran): lipid complex solution; 2 mg/mL patisiran (as patisiran sodium); intravenous [product monograph] Amsterdam (NL): Alnylam Netherlands B.V.; 2019 June 7.
2. Pharmacoeconomic evaluation. In: CDR submission:Onpattro (patisiran), solution for infusion 2 mg/mL [CONFIDENTIAL manufacturer's submission]. Amsterdam (NL): Alnylam Netherlands BV; 2019 Jan 24.
3. CDR submission: Onpattro (patisiran), concentrate for solution for infusion 2 mg/mL [CONFIDENTIAL manufacturer's submission]. Amsterdam (NL): Alnylam Netherlands BV; 2019 Jan 24.
4. Adams D, Gonzalez-Duarte A, O'Riordan WD, et al. Patisiran, an RNAi therapeutic, for hereditary transthyretin amyloidosis. *N Engl J Med.* 2018;379(1):11-21.
5. Guidelines for the economic evaluation of health technologies: Canada. 4th ed. Ottawa (ON): CADTH; 2017: https://www.cadth.ca/dv/guidelines-economic-evaluation-health-technologies-canada-4th-edition. Accessed 2019 Apr 29.
6. Alnylam response to March 1st 2019 CDR request for additional information regarding the Onpattro (patisiran) CDR review [CONFIDENTIAL additional manufacturer's information]. Amsterdam (NL): Alnylam Netherlands B.V.; 2019 Mar 12.
7. Ando Y, Coelho T, Berk JL, et al. Guideline of transthyretin-related hereditary amyloidosis for clinicians. *Orphanet J Rare Dis.* 2013;8:31.
8. Clinical study report: ALN-TTR02-004. APOLLO: a phase 3 multicenter, multinational, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of Patisiran (ALN-TTR02) in transthyretin (TTR)- mediated polyneuropathy (familial amyloidotic polyneuropathy-FAP) [CONFIDENTIAL internal manufacturer's report]. Cambridge (MA): Alnylam Pharmaceuticals, Inc; 2017 Nov 20.
9. Benson MD, Waddington-Cruz M, Berk JL, et al. Inotersen treatment for patients with hereditary transthyretin amyloidosis. *N Engl J Med.* 2018;379(1):22-31.
10. Ruberg FL, Maurer MS, Judge DP, et al. Prospective evaluation of the morbidity and mortality of wild-type and V122I mutant transthyretin amyloid cardiomyopathy: the Transthyretin Amyloidosis Cardiac Study (TRACS). *Am Heart J.* 2012;164(2):222-228.e221.
11. Tegsedi (inotersen): 284 mg inotersen / 1.5 mL per syringe [189 mg inotersen / mL (as inotersen sodium)] injection[product monograph]. Boston (MA): Akcea Therapeutics, Inc. ; 2018 Oct 2.
12. Ackea Therapeutics. Getting started with Tegsedi™. 2018; https://tegsedi.com/wp-content/uploads/2018/11/tegsedi-patient-brochure.pdf. Accessed 2019 May 1.
13. Ionis Pharmaceuticals. Akcea and Ionis Announce Approval of TEGSEDI™ (inotersen injection) in Canada. 2018; http://ir.ionispharma.com/news-releases/news-release-details/akcea-and-ionis-announce-approval-tegseditm-inotersen-injection. Accessed 2019 Apr 18.
14. Clinical study report: ALN-TTR02-003. A phase 2, multicenter, open-label, extension study to evaluate the long-term safety, clinical activity, and pharmacokinetics of ALN-TTR02 in patients with familial amyloidotic polyneuropathy who have previously received ALN-TTR02[CONFIDENTIAL internal manufacturer's report]. Cambridge (MA): Alnylam Pharmaceuticals, Inc.; 2017 Feb 9.
15. Clinical study report: ALN-TTR02-006. A multicenter, open-label, extension study to evaluate the long-term safety and efficacy of Patisiran in patients with familial amyloidotic polyneuropathy who have completed a prior clinical study with Patisiran [CONFIDENTIAL internal manufacturer's report]. Cambridge (MA): Anylam Pharmaceuticals Inc.; 2017 Nov 20.
16. Briggs AH, Ades AE, Price MJ. Probabilistic sensitivity analysis for decision trees with multiple branches: use of the Dirichlet distribution in a Bayesian framework. *Med Decis Making.* 2003;23(4):341 - 350.
17. Ontario Ministry of Health Long-Term Care. Ontario drug benefit formulary/comparative drug index. 2018; https://www.formulary.health.gov.on.ca/formulary/. Accessed 2018 Feb 15.
18. National Institute for Health and Care Excellence. Highly specialised technology evaluation: patisiran for treating hereditary transthyretin amyloidosis [ID1279] evaluation report. 2018; https://www.nice.org.uk/guidance/gid-hst10014/documents/committee-papers. Accessed 2019 Apr 29.
19. National Institute for Health and Care Excellence. Evaluation consultation document: inotersen for treating hereditary transthyretinrelated amyloidosis. 2018; https://www.nice.org.uk/guidance/gid-hst10013/documents/evaluation-consultation-document. Accessed 2019 Apr 29.
20. Product information: Vyndaqel (tafamidis meglumine) *(European public assessment report)*. London (GB): European Medicines Agency; 2011: https://www.ema.europa.eu/en/documents/product-information/vyndaqel-epar-product-information_en.pdf Accessed 2019 Apr 29.
21. McConaghie A. Alnylam's big moment: bringing groundbreaking RNAi drugs to Europe. 2018; http://www.pmlive.com/pharma_intelligence/Alnylams_big_moment_bringing_groundbreaking_RNAi_drugs_to_Europe_1255879. Accessed March 12, 2019.
22. B. C. Government. BC PharmaCare formulary search. 2018; https://pharmacareformularysearch.gov.bc.ca. Accessed 2019 Mar 1.
23. Boston Univeristy. The effect of diflunisal on familial amyloidosis. *Clinicaltrials.gov*. Bethesda (MD): U.S. National Library of Medicine: https://clinicaltrials.gov/ct2/show/NCT00294671. Accessed 2019 Mar 1.

24. Bank of Canada. Daily exchange rates lookup. https://www.bankofcanada.ca/rates/exchange/daily-exchange-rates-lookup/?series%5B%5D=FXGBPCAD&lookupPage=lookup_daily_exchange_rates_2017.php&startRange=2009-04-26&rangeType=range&rangeValue=&dFrom=2018-01-01&dTo=2018-12-31&submit_button=Submit. Accessed April 26, 2019.
25. National Institute for Health and Care Excellence. Evaluation consultation document: patisiran for treating hereditary transthyretin-related amyloidosis. 2018; https://www.nice.org.uk/guidance/gid-hst10014/documents/evaluation-consultation-document. Accessed 2019 Apr 29.
26. Adams D, Buades J, Suhr O, Obici L, Coelho T. Preliminary assessment of neuropathy progression in patients with hereditary ATTR amyloidosis after orthotopic liver transplantation (OLT). *Orphanet J Rare Dis.* 2015;10(1):P19.
27. Adams D, Suhr OB, Dyck PJ, et al. Trial design and rationale for APOLLO, a Phase 3, placebo-controlled study of patisiran in patients with hereditary ATTR amyloidosis with polyneuropathy. *BMC Neurol.* 2017;17(1):181.
28. Adams D, Suhr OB, Conceicao I, et al. Phase 2 open-label extention (OLE) study of patisiran, an investigational siRNA agent for familial amyloidotic polyneuropathy (FAP). *Orphanet J Rare Dis.* 2015;10(73).
29. Kristen AV, Maurer MS, Rapezzi C, Mundayat R, Suhr OB, Damy T. Impact of genotype and phenotype on cardiac biomarkers in patients with transthyretin amyloidosis - report from the Transthyretin Amyloidosis Outcome Survey (THAOS). *PLoS One.* 2017;12(4):e0173086.
30. Grogan M, Scott CG, Kyle RA, et al. Natural history of wild-type transthyretin cardiac amyloidosis and risk stratification using a novel staging system. *J Am Coll Cardiol.* 2016;68(10):1014-1020.
31. Damy T, Jaccard A, Guellich A, et al. Identification of prognostic markers in transthyretin and AL cardiac amyloidosis. *Amyloid.* 2016;23(3):194-202.
32. Ternacle J, Bodez D, Guellich A, et al. Causes and consequences of longitudinal LV dysfunction assessed by 2D strain echocardiography in cardiac amyloidosis. *JACC Cardiovasc Imaging.* 2016;9(2):126-138.
33. Palladini G, Campana C, Klersy C, et al. Serum N-terminal pro-brain natriuretic peptide is a sensitive marker of myocardial dysfunction in AL amyloidosis. *Circulation.* 2003;107(19):2440-2445.
34. Lehrke S, Steen H, Kristen AV, et al. Serum levels of NT-proBNP as surrogate for cardiac amyloid burden: new evidence from gadolinium-enhanced cardiac magnetic resonance imaging in patients with amyloidosis. *Amyloid.* 2009;16(4):187-195.
35. Kristen AV, Biener M, Hegenbart U, et al. Evaluation of the clinical use of midregional pro-atrial natriuretic peptide (MR-proANP) in comparison to N-terminal pro-B-type natriuretic peptide (NT-proBNP) for risk stratification in patients with light-chain amyloidosis. *Int J Cardiol.* 2014;176(3):1113-1115.
36. Sullivan PW, Ghushchyan V. Preference-based EQ-5D index scores for chronic conditions in the United States. *Med Decis Making.* 2006;26(4):410-420.
37. National Institute for Health and Care Excellence. Public observer slides: Ocrelizumab for treating relapsing multiple sclerosis 2018; https://www.nice.org.uk/guidance/ta533/documents/1. Accessed 2019 Apr 8.
38. Ratcliffe J, Longworth L, Young T, Bryan S, Burroughs A, Buxton M. Assessing health-related quality of life pre- and post-liver transplantation: a prospective multicenter study. *Liver Transpl.* 2002;8(3):263-270.
39. Karabulut A, Kaplan A, Aslan C, Iltumur K, Toprak G, Toprak N. The association between NT-proBNP levels, functional capacity and stage in patients with heart failure. *Acta Cardiol.* 2005;60(6):631-638.
40. Statistics Canada. Life tables, Canada, provinces and territories, 1980/1982 to 2014/2016. 2019; https://www150.statcan.gc.ca/n1/en/catalogue/84-537-X. Accessed 2019 Apr 18.
41. Ericzon BG, Wilczek HE, Larsson M, et al. Liver transplantation for hereditary transthyretin amyloidosis: after 20 years still the best therapeutic alternative? *Transplantation.* 2015;99(9):1847-1854.
42. Coelho T, Ericzon B-g, Falk Rea. A guide to transthyretin amyloidosis. Clarkston (MI): Amyloidosis Foundation; 2016: http://www.amyloidosis.org/wp-content/uploads/2017/05/2017-ATTR-guide.pdf. Accessed 2019 Apr 1.
43. Ontario Ministry of Health Long-Term Care. Schedule of benefits for laboratory services. 2017; http://www.health.gov.on.ca/en/pro/programs/ohip/sob/lab/lab_mn2018.pdf. Accessed 2019 Apr 29.
44. Ontario Ministry of Health Long-Term Care. Schedule of benefits for physician services under the Health Insurance Act: effective December 21, 2015. Toronto (ON): The Ministry of Health and Long-Term Care; 2015: http://www.health.gov.on.ca/english/providers/program/ohip/sob/physserv/physserv_mn.html. Accessed 2019 Apr 29.
45. Common drug review: pharmacoeconomic review report: alemtuzumab (Lemtrada, intravenous). Ottawa (ON): CADTH; 2015: https://www.cadth.ca/sites/default/files/cdr/pharmacoeconomic/SR0405_Lemtrada_RRMS_PE_Report.pdf. Accessed 2019 Apr 29.
46. Ontario case costing initiative (OCCI). Toronto (ON): Ontario Health and Long-Term Care; 2018: https://www.ontario.ca/data/ontario-case-costing-initiative-occi. Accessed 2019 Apr 29.
47. Bank of Canada. Inflation calculator. 2018; http://www.bankofcanada.ca/rates/related/inflation-calculator/. Accessed 2019 Apr 9.