PATISIRAN (ONPATTRO — ALNYLAM NETHERLANDS BV)
Indication: For the treatment of polyneuropathy in adult patients with hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis).

RECOMMENDATION
The CADTH Canadian Drug Expert Committee (CDEC) recommends that patisiran be reimbursed for the treatment of polyneuropathy in adult patients with hATTR amyloidosis only if the following conditions are met.

Conditions for Reimbursement

Initiation Criteria
1. Confirmed genetic diagnosis of hATTR.
2. Patients who have all of the following characteristics:
   2.1 are symptomatic with early-stage neuropathy, defined as
      2.1.1 polyneuropathy disability [PND] stage I to ≤ IIIB, or
      2.1.2 familial amyloidotic polyneuropathy [FAP] stage I or II
   2.2 do not exhibit severe heart failure symptoms (defined as New York Heart Association [NYHA] class III or IV)
   2.3 have not previously undergone a liver transplant.
3. Patisiran should not be used in combination with other interfering ribonucleic acid drugs or transthyretin stabilizers used to treat hATTR.

Discontinuation Criteria
1. An initial assessment of treatment response should occur nine months after treatment initiation. Thereafter, patients should be assessed at least every six months to determine whether they would benefit from continued treatment with patisiran.
2. Treatment with patisiran should be discontinued for patients who are:
   2.1 permanently bedridden and dependent on assistance for basic activities of daily living, or
   2.2 receiving end-of-life care.

Prescribing Conditions
1. The patient must be under the care of a specialist with experience in the diagnosis and management of hATTR.

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

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Reasons for the Recommendation

1. In one double-blind, placebo-controlled, phase III study (APOLLO) in adult patients with hATTR with documented gene mutation, patisiran was associated with a statistically significant improvement compared with placebo in neurological function after 18 months, measured using the Modified Neurologic Impairment Score + 7 (mNIS+7) composite score, and in health-related quality of life (HRQoL), based on the Norfolk Quality of Life-Diabetic Neuropathy (Norfolk QoL-DN) questionnaire. Statistically significant differences were also demonstrated favouring patisiran for disability (measured using the Rasch-built Overall Disability Scale [R-ODS]), gait speed (measured by the 10 metre walk test), unintended weight loss (measured by modified body mass index [mBMI]), and autonomic symptoms (measured by the Composite Autonomic Symptom Score [COMPASS]-31 instrument). The effect size for gait speed was both clinically and statistically significant, while the effect sizes for other main study measures were challenging to interpret as a clinically important difference has not been defined.
2. There is an unmet need for the treatment of polyneuropathy in patients with hATTR. Current treatments (liver transplant and dlfunisal) are associated with limitations.
3. All patients in the APOLLO study were classified as having early neuropathy (PND stage ranging from I to IIIIB). Approximately half of the patients randomized to treatment with patisiran were classified as FAP stage I and the other half were classified as FAP stage II. All patients had an NYHA class of either I or II; patients with an NYHA class of III or IV were excluded from the study. The only evidence available to assess the effects of patisiran in patients with more severe polyneuropathy than those patients studied in APOLLO was available from the phase II (ALN-TTR02-003) and phase III (ALN-TTR02-006) extension studies; however, this evidence is of insufficient quality to support a listing recommendation.
4. Patients with a prior liver transplant were excluded from the APOLLO trial; therefore, there is no evidence to support the use of patisiran in this patient population.

5. The manufacturer-submitted price of patisiran is $13,022 per vial, with an annual cost between $451,430 and $677,145 per patient. Based on the population considered by CDEC (which is aligned with the clinical trial population), the incremental cost-utility ratio (ICUR) for patisiran compared with best supportive care (BSC) was greater than $4.8 million per quality-adjusted life-year (QALY). Patisiran is not considered to be cost-effective at the manufacturer’s submitted price. A large reduction in price (98%) is required for patisiran to achieve an ICUR of $50,000 per QALY based on the CADTH best estimate.

Implementation Considerations

- Genetic testing is required to confirm a diagnosis of hATTR in order to differentiate this condition from other causes of amyloidosis.
- PND is classified according to the following stages: stage 0: no symptoms; stage I: sensory disturbances but preserved walking capability; stage II: impaired walking capacity but ability to walk without a stick or crutches; stage IIIA: walking with the help of one stick or crutch; stage IIIB: walking with the help of two sticks or crutches; stage IV: confined to a wheelchair or bedridden.
- FAP is classified according to the following stages: stage 0: no symptoms; stage I: unimpaired ambulation, mostly mild sensory, motor, and autonomic neuropathy in the lower limbs; stage II: assistance with ambulation required, mostly moderate impairment progression to the lower limbs, upper limbs, and trunk; stage III: wheelchair bound or bedridden, severe sensory, motor, and autonomic involvement of all limbs.

Discussion Points

- The committee discussed whether the patient population eligible for treatment with patisiran should be based on the inclusion criteria of the APOLLO clinical trial, or whether it would be appropriate to initiate treatment in patients with advanced polyneuropathy (i.e., PND stage IV or FAP stage III). There is no rigorous evidence for initiating patisiran in a patient population with more advanced polyneuropathy and more data are required to determine if such patients would benefit from treatment. Similarly, there are no data to assess the effects of patisiran in presymptomatic patients with a confirmed genetic mutation. The clinical experts consulted by CADTH for this review were of the opinion that it would be inappropriate to treat these presymptomatic patients with patisiran due to the heterogeneous nature of hATTR amyloidosis’s progression and severity.
- Two long-term open-label extension studies were available for this review. The phase II extension study (ALN-TTR02-003) included 27 patients who were treated with patisiran for two years. The phase III extension study (ALN-TTR02-006) is ongoing and will continue to assess the safety and efficacy of patisiran for up to five years; however, at the time of the interim analysis available for this review, only approximately 35% of enrolled patients had completed the 52-week efficacy assessment. Both studies are limited by the absence of a comparator group, lack of blinding, and small sample sizes; therefore, the longer-term benefit of patisiran remains uncertain. Clinicians using patisiran to treat polyneuropathy in patients with hATTR should be strongly encouraged to enroll patients in ATTR registries to track outcomes and evaluate the long-term effectiveness and safety of patisiran.
- In the open-label phase II (ALN-TTR02-003) and phase III (ALN-TTR02-006) extension trials, some patients received concomitant therapy with tafamidis or diflunisal in addition to patisiran. However, these trials were associated with substantial limitations and ALN-TTR02-006 is ongoing. More data are required to support or refute the efficacy of combination therapy.
- Given the heterogeneous presentation of the disease, there is potential for use of patisiran in a broad patient population, such as those presenting with cardiac disease manifestations. The APOLLO study examined a number of cardiac biomarkers (N-terminal-pro brain-type natriuretic peptide [NT-proBNP], troponin I) and echocardiogram parameters (left ventricular ejection fraction, left ventricular wall thickness, longitudinal strain) to explore the impact of patisiran on cardiac structure and function; however, it is unclear if these measures represent a direct clinical benefit in patients with hATTR. Further, these exploratory measures were outside the statistical testing hierarchy and the data were associated with numerous limitations, including marked imbalances in cardiac involvement at baseline. Therefore, the potential benefit of patisiran on cardiac outcomes in patients with hATTR remains uncertain.
- Given the high cost of patisiran, the committee felt that having an objective measure of efficacy was essential to support ongoing reimbursement. In the pivotal APOLLO study, the primary outcome of neurologic impairment was measured using the mNIS+7. However, the experts consulted for this review stated that the mNIS+7 is not used in clinical practice to monitor patients and that some components, such as quantitative sensory testing, are not available in all centres.
Background

Patisiran has a Health Canada indication for the treatment of polyneuropathy in adult patients with hATTR amyloidosis. Patisiran is a double-stranded small interfering ribonucleic acid formulated as lipid nanoparticles. It is available as a 2 mg/mL lipid complex solution for IV administration (5 mL solution in a 10 mL single-use vial) that must be diluted and infused over 80 minutes. The recommended dosage is 0.3 mg/kg IV once every three weeks, with a maximum dose of 30 mg for patients who weigh 100 kg or greater.

Summary of Evidence Considered by CDEC

The committee considered the following information prepared by the CADTH Common Drug Review: a systematic review of randomized controlled trials of patisiran, two indirect treatment comparisons (ITCs), and a critique of the manufacturer’s pharmacoeconomic evaluation. The committee also considered input from a panel of clinical experts considered specialists in treating patients with hATTR, and patient group—submitted information about outcomes and issues important to patients.

Summary of Patient Input

One patient group, the Canadian Organization for Rare Disorders (CORD), provided input for this submission. Patient perspectives were obtained from an online survey, individual interviews, and written testimonials. CORD disclosed receiving financial support in the past two years from the manufacturer of patisiran. The following is a summary of key input from the perspective of the patient groups:

- hATTR is a rare, inherited, progressive, debilitating, potentially fatal condition that affects multiple systems in the body. It results in significant physical damage, pain, and psychological distress, and impacts daily functioning and HRQoL.
- The currently available treatments for hATTR generally manage symptoms, but do not address the disease course. Many patients will continue to progress after liver transplantation or with diffunisal therapy. Other treatments are supportive and may help minimize symptoms related to peripheral neuropathy, and cardiac or gastrointestinal manifestations.
- Patients expect that patisiran will slow or halt disease progression and may improve symptoms associated with hATTR.

Clinical Trials

The systematic review included one double-blind, randomized, placebo-controlled, phase III trial of adults with hATTR with documented transthyretin mutation and polyneuropathy who were classified as PND stage IIIB or lower (i.e., were able to walk with two sticks or crutches). Patients were randomized (2:1) to patisiran 0.3 mg/kg or placebo IV every three weeks for 18 months (N = 225). The objective was to determine the superiority of patisiran versus placebo on the change from baseline to 18 months on neurological impairment as measured by the mNIS+7. In the APOLLO study, 7% versus 29% of patients withdrew from the trial, and 7% versus 38% stopped treatment early in the patisiran and placebo groups, respectively.

The APOLLO study was not designed to evaluate mortality, cardiac morbidity, or hospitalizations, which are important outcomes to patients. No active comparator trials were identified.

Outcomes

Outcomes were defined a priori in the CADTH Common Drug Review systematic review protocol. Of these, the committee discussed the following: HRQoL, neuropathic impairment, disability, functional status, nutritional status, and autonomic symptoms.

The primary outcome was the change from baseline to 18 months in the mNIS+7.

- HRQoL was measured using the Norfolk Quality of Life – Diabetic Neuropathy (Norfolk QoL-DN) questionnaire, which is a standardized 35-item patient-reported outcomes measure that assesses the impacts of neuropathy on functional status. It includes five domains: physical functioning/large-fibre neuropathy, activities of daily living, symptoms, small-fibre neuropathy, and autonomic neuropathy. The domains are aggregated to provide a total score (range –4 to 136), with higher scores representing poorer health status. In patients with hATTR, the Norfolk QoL-DN showed moderate-to-high correlation with objective measures of neurologic function, discriminant validity, and acceptable test-retest reliability.
The mNIS+7 is a 304-point composite measure of neurologic impairment that includes the following measures and components: physical exam of lower limbs, upper limbs, and cranial nerves in order to assess motor strength and weakness and determine the component score for NIS-weakness (192 points total) and NIS-reflexes (20 points); sensory testing to determine the quantitative sensory testing score, including assessing touch pressure by body surface area and heat pain by body surface area (80 points); electrophysiologic measures of small and large nerve fibre function in order to determine the sum of five nerve conduction studies component score (10 points); postural blood pressure measurement to assess autonomic function (2 points). Higher scores indicate greater impairment.

Disability was assessed using the R-ODS, a 24-item scale that captures activity and social participation limitations in patients. It is scored from 0 to 48 with 0 being the worst disability and 48 the best (no limitations).

The 10 metre walk test measures functional mobility and walking speed in metres per second over the short distance. In patients who survived a stroke or older adults with mobility difficulties, a change of 0.05 metres per second (m/s) was estimated as a minimal clinically important difference (MCID).

The nutritional status of patients was evaluated using the mBMI; calculated as the product of body mass index (weight in kilograms divided by the square of height in metres) and serum albumin (g/L).

COMPASS-31 is a patient-reported measure to assess changes in autonomic symptoms. It consists of 31 questions that evaluate six domains: orthostatic intolerance, vasomotor, secretomotor, gastrointestinal, bladder, and pupillomotor. Scores range from 0 to 100 with higher scores representing more severe symptoms.

Efficacy

Although identified as key efficacy outcomes of interest in this review, the APOLLO study was not designed to assess mortality, cardiovascular morbidity, or hospitalizations as efficacy end points. Seven patients in the patisiran group (5%) and six patients in the placebo group (8%) died during the APOLLO study.

Patisiran was associated with statistically significant differences versus placebo for the change from baseline to 18 months in the Norfolk QoL-DN instrument (least squares [LS] mean difference of −21.1 points; 95% confidence interval [CI], −27.2 to −15.0; \( P < 0.0001 \)) (MCID unknown).

The change from baseline in mNIS+7 score, the primary outcome in the APOLLO study, was also statistically significant, favouring patisiran, with an LS mean difference of −34.0 points; 95% CI, −39.9 to −28.1; \( P < 0.0001 \). The results of the NIS-weakness, (a subscale of the mNIS+7) were also statistically significant, with an LS mean difference of −17.9 points; 95% CI, −22.3 to −13.4 points; \( P < 0.0001 \). No MCID was found in the literature for the mNIS+7 or NIS-weakness.

All other secondary outcomes within the statistical testing hierarchy showed statistically significant differences favouring patisiran versus placebo in the change from baseline to 18 months:

- R-ODS: LS mean difference of 9.0 points; 95% CI, 7.0 to 10.9; \( P < 0.0001 \) ; MCID unknown.
- 10 metre walk test: LS mean difference of 0.31 m/s; 95% CI, 0.23 to 0.39; \( P < 0.0001 \). The differences exceeded the MCID of 0.05 m/s that has been reported in the literature.
- mBMI: LS mean difference of 116; 95% CI, 82 to 149; \( P < 0.0001 \). No known MCID.
- COMPASS-31: LS mean difference of −7.5; 95% CI, −11.9 to −3.2; \( P = 0.0008 \). No MCID was identified in the literature.

The primary and key secondary outcomes showed a consistent pattern of treatment effects, with mean scores in the patisiran group remaining stable over 18 months, and the scores in the placebo group suggesting a decline in the patients’ disease status.

Harms (Safety)

- In the APOLLO study, most patients (97%) experienced an adverse event (AE), with diarrhea, peripheral edema, and infusion-related reactions reported most frequently among those who received patisiran.
• The percentage of patients who reported a serious AE was similar for the patisiran (37%) and placebo (40%) groups, but the percentage of patients who stopped treatment due to AEs was lower in the patisiran group than in the placebo group (5% versus 14%).

• Infusion-related reactions were reported more frequently in the patisiran than placebo group (19% versus 9%); however, only one patient treated with patisiran stopped treatment due to these events and no events met the criteria for a serious AE. The most common infusion-related reactions in the patisiran group were back pain, abdominal pain, headache, arthralgia, and dyspnea. Flushing was the most common infusion-related reaction in the placebo group. Some of these AEs were associated with pre-medications administered prior to the infusions, which included corticosteroids, acetaminophen, histamine-2 receptor, and histamine-1 receptor blockers. A reduced premedication regimen was implemented in these patients with no increase in infusion-related reactions.

• The APOLLO study had limited power to detect infrequent AEs, or those with a longer lag time. Considering that patisiran is part of a new drug class, and controlled data were limited to a single randomized controlled trial that was 18 months in duration, additional data are required to determine the safety of the drug in the longer term.

Indirect Treatment Comparisons
The manufacturer submitted an ITC that compared patisiran with inotersen, based on data from two phase III trials (APOLLO and NEURO-TTR). In this analysis, individual patient data from APOLLO was used to calculate the mNIS+7oni, a composite that used different sensory and autonomic testing than the mNIS+7 in APOLLO, but the same NIS-weakness, NIS-reflexes, and nerve conduction studies. Two indirect comparisons were calculated; one using the Bucher method, and a second using matching-adjusted indirect comparison methods. Both analyses suggested that patisiran was statistically superior to inotersen for the change from baseline in mNIS+7oni and the Norfolk QoL-DN scores. Although the differences between treatments were statistically significant, the clinical significance of the differences is unclear, given the lack of MCID for these outcome measures. A second indirect comparison comparing patisiran with tafamidis was identified in the literature, but due to differences in the patient populations and outcome measures, the results carry a high level of uncertainty and no strong conclusions could be drawn from this analysis.

Cost and Cost-Effectiveness
Patisiran is administered as an intravenous infusion at a dose of 0.3 mg/kg (to a maximum of 30 mg) once every three weeks. At the manufacturer’s submitted price of $13,022 for a single-use 2 mg/mL of 5 mL solution in a single-use 10 mL vial, patisiran has an average annual drug cost 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 needed.

The manufacturer submitted a cost-utility analysis comparing patisiran with inotersen in the base case, for the treatment of polyneuropathy in patients with hATTR. A comparison with BSC was made in a scenario analysis. A Markov model with health states defined by PND scores, NT-proBNP levels (greater than or equal to 3,000 pg/mL was associated with higher cardiac involvement), orthotopic liver transplantation, and death was used to model disease progression. Patients entered the model, with distributions for NT-proBNP and PND values reflecting the APOLLO trial, and were assumed to receive treatment for the entire model time horizon. Transition probabilities comparing patisiran with inotersen were estimated from the manufacturer’s ITC. Transition probabilities comparing patisiran with BSC were estimated directly from the APOLLO trial. Treatment and time-dependent health state utilities were estimated by regression of EuroQol 5-Dimensions data from the APOLLO trial. Health state costs were estimated from a Delphi panel of UK physicians. CADTH identified several key limitations with the manufacturer’s economic submission:

• different estimates of the efficacy for patisiran were used in the model depending on which comparator was selected, resulting in different estimated total costs and QALYs for patisiran depending on whether it was compared with inotersen or BSC

• health states used in the model did not capture all aspects of the condition; therefore, the manufacturer applied treatment-specific utility values and health state costs

• caregiver impacts are not appropriate for the public payer perspective

• health state and administration costs were not representative of Canadian public payers

• uncertainty in the effect of patisiran on cardiac-related outcomes

• uncertainty in the price of inotersen
- incomplete adherence with patisiran was assumed, based on the APOLLO trial, while perfect adherence was assumed for inotersen
- long-term effectiveness of patisiran is uncertain.

CADTH reanalyses accounted for some of the identified limitations (i.e., making changes to the model such that the clinical effects of patisiran do not change by comparator, which also facilitates sequential analysis; assuming no difference in treatment-specific utilities or health state costs; removing caregiver disutility; removing health state costs that are not covered by Canadian payers: removing administration costs for inotersen and reducing administration costs for patisiran; revising liver transplant costs; removing the treatment effect of patisiran on cardiac outcomes; assuming a drug cost for inotersen based on the relative costs of patisiran and inotersen in the UK; assuming 100% treatment adherence; and, changing baseline characteristics to match those observed in the APOLLO trial). This resulted in an estimated ICUR for patisiran of $4,818,778 per QALY gained compared with BSC. Inotersen was extendedly dominated by patisiran (i.e., inotersen was less effective and more costly than a combination of patisiran and BSC). To be considered cost-effective at a willingness-to-pay threshold of $50,000 per QALY, a 98% reduction in the price of patisiran would be required.

**CDEC Members**

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**June 19, 2019 Meeting**

**Regrets**

None

**Conflicts of Interest**

None