CADTH

CADTH COMMON DRUG REVIEW

CADTH Canadian Drug Expert Committee Recommendation

(Final)

INOTERSEN (TEGSEDI — AKCEA THERAPEUTICS, INC.)
Indication: Treatment of polyneuropathy in adults with hereditary transthyretin-mediated amyloidosis (hATTR)

RECOMMENDATION
The CADTH Canadian Drug Expert Committee recommends that inotersen be reimbursed for the treatment of polyneuropathy in adult patients with hATTR, 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 stage I to ≤ IIIB, or
     - 2.1.2 Familial amyloidotic polyneuropathy stage I or II.
   - 2.2 Do not exhibit severe heart failure symptoms (defined as New York Heart Association class III or IV).
   - 2.3 Have not previously undergone a liver transplant.
3. Inotersen 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 inotersen.
2. Treatment with inotersen 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
The patient must be under the care of a specialist with experience in the diagnosis and management of hATTR.

Pricing conditions
Reduction in price.

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Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that inotersen be reimbursed for the treatment of polyneuropathy in adult patients with hATTR, 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. Inotersen 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 inotersen.
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   - 2.1. Permanently bedridden and dependent on assistance for basic activities of daily living, or
   - 2.2. Receiving end-of-life care.

Prescribing conditions

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

Pricing conditions

Reduction in price.

Reasons for the Recommendation

1. One double-blind, phase II/III, randomized controlled trial (RCT) (NEURO-TTR, N = 172) in adult patients with hATTR with documented gene mutation and amyloid deposits demonstrated that inotersen is associated with a statistically significant slower decline in neurological function, measured using the modified Neuropathy Impairment Score + 7 (Ionis version; mNIS+7_{Ionis}) composite score (least squares mean [LSM] difference between groups, –19.73 points; 95% confidence interval [CI], –26.43 to –13.03) compared with placebo at 66 weeks. Inotersen also improved health-related quality of life (HRQoL), based on the Norfolk Quality of Life-Diabetic Neuropathy Questionnaire (Norfolk QoL-DN; LSM difference: –11.68 points; 95% CI, –18.29 to –5.06), compared with placebo at 66 weeks.
2. There is an unmet need for effective treatments for polyneuropathy in patients with hATTR. No other indicated effective treatments (i.e., patisiran) are currently reimbursed.
3. Patients in the NEURO-TTR study were classified as having early neuropathy. Approximately two-thirds of the patients randomized to treatment with inotersen were classified as equivalent to FAP stage I and the other one-third were classified as equivalent to FAP stage II. There is currently no evidence available to assess the effects of inotersen in patients with more severe polyneuropathy than those patients studied in NEURO-TTR.
4. Patients with a prior liver transplant were excluded from the NEURO-TTR trial, so there is no evidence to support the use of inotersen in this patient population.
5. The manufacturer submitted price of inotersen is $8,076.92 per prefilled syringe, with an annual cost of approximately $420,000 per patient. Based on the population considered by CDEC (which is aligned with the clinical trial population), the incremental

cost-utility ratio (ICUR) for inotersen compared with best supportive care (BSC) was greater than $1.3 million per quality-adjusted life-year (QALY). Inotersen is not considered to be cost-effective at the manufacturer's submitted price. Several limitations to the model could not be addressed and a reduction in price of at least 88% is required for inotersen 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.
- Polyneuropathy stage in the NEURO-TTR study was categorized according to the Coutinho staging system. Coutinho stage I polyneuropathy (i.e., does not require assistance with ambulation) corresponds to FAP stage I and PND stage I and stage II. Coutinho stage II polyneuropathy (i.e., requires assistance with ambulation) corresponds to FAP stage II and PND stage IIIa and stage IIIb. Lastly, Coutinho stage III polyneuropathy (i.e., wheelchair bound or bedridden) corresponds to FAP stage III and PND stage IV.

Discussion Points

- The committee noted that the Health Canada indication for inotersen was based on the patient population eligible for and enrolled into the NEURO-TTR study, representing those with early-stage polyneuropathy. There are no data to assess the effects of inotersen outside of the studied population, including in presymptomatic patients with a confirmed genetic mutation. The clinical experts consulted by CADTH for this review believed it would be inappropriate to treat these presymptomatic patients due to the heterogeneous nature of disease progression and severity.
- Key limitations in NEURO-TTR were discussed by CDEC.
  - A range of 12% to 25% of patients in the placebo group and 19% to 31% of patients in the inotersen group were excluded from statistical analyses of efficacy outcomes at week 65 or week 66, depending on the outcome analyzed. Several sensitivity analyses of the primary outcomes (i.e., the mNIS+7$_{Ionis}$ composite score and Norfolk QoL-DN questionnaire) indicated that the results were sensitive to missing data and that the true magnitude of treatment effect with inotersen may be smaller than what was observed with the primary analysis. However, the between group difference on the mNIS+7$_{Ionis}$ composite score remained statistically significant with more conservative analysis methods. As well, the more conservative estimate exceeded a between group difference of 10 points that CDEC considered appropriate to conclude the effects of inotersen would be relevant to patients.
  - A disproportionate number of patients treated with inotersen (51% versus 12% with placebo) in NEURO-TTR experienced injection site reactions that may have led patients or investigators to accurately determine that an active treatment was being administered. This potential unblinding of treatment assignment may have led to bias in the subjectively assessed outcome measures, such as the Norfolk QoL-DN questionnaire, which was a primary efficacy outcome, with the direction of bias in favour of inotersen if patients believed that active treatment would improve their condition.
- There is limited long-term evidence for the efficacy and safety of inotersen. One long-term, single-group, open-label extension study (Study CS3) was discussed by the committee. The extension study is ongoing (planned for up to five years) and only interim analyses (approximately 72% of enrolled patients had data available at the 52-week efficacy assessment point) were available for CDEC to consider. The longer-term evidence was also limited by the absence of a comparator group, lack of blinding, and small sample size; therefore, there is currently insufficient data to determine the longer-term effects of inotersen. Clinicians using inotersen to treat polyneuropathy in patients with hATTR should be strongly encouraged to enroll patients in transthyretin-mediated amyloidosis registries to track outcomes and evaluate longer-term effectiveness and safety of inotersen.
- Given the heterogeneous presentation of the disease, there is potential for use of inotersen in a broad patient population, such as those presenting with cardiac disease manifestations (e.g., cardiomyopathy). All patients enrolled in NEURO-TTR had an

NYHA class of either I or II; patients with an NYHA class of III or IV were excluded from the study. The study examined a number of cardiac biomarkers (N-terminal-pro brain-type natriuretic peptide [NT-proBNP]) and echocardiogram parameters (left ventricular ejection fraction [LVEF], left ventricular [LV] wall thickness, longitudinal strain) to explore the impact of inotersen on cardiac structure and function; however, it is unclear if these measures represent direct clinical benefit in patients with hATTR. Further, there were no statistically significant differences between inotersen and placebo on these outcome measures. Therefore, the potential benefit of inotersen on cardiac outcomes in patients with hATTR remains uncertain.

- Given the high cost of inotersen, the committee felt that having an objective measure of efficacy was essential to support ongoing reimbursement. In the pivotal NEURO-TTR study, the primary outcome of neurologic impairment was measured using the mNIS+7_{Ionis}. However, the experts consulted by CADTH stated that the mNIS+7_{Ionis} is not used in clinical practice to monitor patients and some components, such as quantitative sensory testing, are not available in all centres.
- More patients in the inotersen group of NEURO-TTR experienced serious adverse events (SAEs; 32% versus 22%) and discontinued treatment due to adverse events (AEs; 14% versus 3%) compared with placebo. Thrombocytopenia and glomerulonephritis are of greatest concern for safety, but the risk of these issues may be mitigated by the treatment initiation and monitoring plans detailed in the product monograph for inotersen.
- There are no head-to-head or indirect comparative data between inotersen and other treatments for polyneuropathy related to hATTR. Therefore, the comparative effectiveness and safety of inotersen are currently unknown.

Background

Inotersen has a Health Canada indication for the treatment of stage I or stage II polyneuropathy in adults with hATTR. Inotersen is an antisense oligonucleotide that targets human transthyretin messenger ribonucleic acid. It is available as a subcutaneous injection and the Health Canada–approved dosage is 300 mg (equivalent to 284 mg of parent acid) once weekly.

Summary of Evidence Considered by CDEC Considerations

CDEC considered the following information prepared by the CADTH Common Drug Review: a systematic review of RCTs of inotersen 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, Hereditary Amyloidosis Canada, provided input for this submission. Patient perspectives were obtained from an online survey that included responses from 13 patients with hATTR and a telephone interview of six patients and one caregiver who had experience with inotersen. The following is a summary of key input from the perspective of the patient group:

- hATTR is a rare, progressive, debilitating, fatal condition that affects multiple systems in the body. It results in significant physical damage, pain, psychological distress, and has an impact on daily functioning and HRQoL.
- Patients reported inadequate responses with currently available treatments for hATTR and barriers to obtaining access. The currently available treatments for hATTR generally manage symptoms, but do not address the disease course and patients underscored the significant unmet need for disease-specific treatment options.
- Patients expressed the hope that inotersen would provide neuropathy symptom relief (primarily from pain), improve quality of life, and slow disease progression. Two of six patients who had used inotersen had been using it for more than four years and reported experiencing a significant improvement in their quality of life.

Clinical Trials

The systematic review included one phase II/III combined double-blind, placebo controlled, RCT in 172 patients classified as having Coutinho stage I (i.e., does not require assistance with ambulation) or stage II (i.e., requires assistance with ambulation) polyneuropathy with hATTR (NEURO-TTR). Patients with previous liver transplant, NYHA class III or IV, Coutinho stage III polyneuropathy, and anticipated survival of less than two years were excluded. Patients were randomized in a 2:1 ratio to inotersen 300 mg (N = 112) or placebo (N = 60) once weekly for 65 weeks.

More patients in the inotersen group discontinued treatment than in the placebo group (23.0% versus 13.3%). The primary reason for discontinuation was an adverse event, which occurred more frequently in patients who received inotersen (14.2% versus 1.7%). There were baseline differences in neuropathy and cardiomyopathy (patients in the inotersen group had more severe disease), suggesting that randomization or allocation may have been compromised. Although the study was double-blinded, about a third of patients who received inotersen experienced injection site erythema and a fifth experienced injection site pain, whereas in the placebo group injection site reactions were experienced at a much lower incidence. The presence of an injection site reaction may have led patients or investigators to accurately guess that an active treatment was being administered. No active comparator trials were available.

Outcomes

Outcomes were defined a priori in the CADTH Common Drug Review systematic review protocol. Of these, CDEC discussed the following:

- Norfolk QoL-DN: A self-administered patient-reported instrument to assess the impact of neuropathy on functional status. It is a disease-specific HRQoL instrument. The instrument was originally developed for patients with diabetic neuropathy and has been validated in patients with hATTR. A minimal clinically important difference (MCID) for the Norfolk QoL-DN has not been identified.
- The Short Form-36 version 2 (SF-36v2): A generic HRQoL measure that consists of two composite scores, the Physical Component Summary score and the Mental Component Summary score, and the following eight domain scores: physical function, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health. In general, a change of two points on the Physical Component Summary and three points on the Mental Component Summary of the SF-36v2 indicates a clinically meaningful improvement as determined by the patient. The reliability and validity of the SF-36v2 have been demonstrated in various conditions; however, not in patients with hATTR.
- mNIS+7$_{Ionis}$: A composite outcome of neurological function. The mNIS+7$_{Ionis}$ was developed specially for the monitoring of polyneuropathy in patients with hATTR and has been validated, although no anchor-based MCID was identified.
- The Neuropathy Symptoms and Change Score (NSC): A patient questionnaire that consists of five symptom domains: muscle weakness; sensory – hypo/loss of sensation; sensory – paresthesia/hypersensation; autonomic – gastrointestinal and urinary incontinence; and autonomic – non-gastrointestinal or urinary incontinence. No information was available on the reliability, responsiveness, or MCID of the NSC in patients with hATTR or other neurological conditions.
- The Polyneuropathy Disability (PND) score: The PND is used by physicians to classify hATTR and is primarily based on ambulation.
- Modified body mass index (mBMI): The mBMI corrects for hypoalbuminemia and edema and may reflect nutritional status more accurately than body mass index in conditions such as hATTR that are affected by wasting.
- Cardiac structure and function: These were tested using echocardiogram and N-terminal prohormone of brain natriuretic peptide.
- Harms.

The primary outcomes in NEURO-TTR were a composite of mNIS+7$_{Ionis}$ and Norfolk QoL-DN at week 66.

NEURO-TTR captured outcomes that were mentioned by patients as important, such as impairment in the ability to carry out daily activities, neuropathy, autonomic dysfunction, HRQoL, and impacts on mental health. However, no data were available specifically for pain, fatigue, dizziness, shortness of breath, or leg swelling, which were mentioned as severe or incapacitating by most patients in the input provided to CADTH. There were also no data available to assess whether inotersen reduces hospitalization or improves survival.

Efficacy

At week 66, the LSM difference in change from baseline for the Norfolk QoL-DN between inotersen and placebo was −11.68 points, (95% CI, −18.29 to −5.06; statistically significant in favour of inotersen). In a sensitivity analysis that included all randomized patients and conservatively imputed missing data, the LSM difference in change from baseline for the Norfolk QoL-DN remained statistically significant in favour of inotersen (−8.56 points; 95% CI, −15.42 to −1.71). No MCID has been established for the Norfolk QoL-DN so it is difficult to conclude whether or not the observed difference is clinically meaningful.

At week 66, the LSM difference in change from baseline for the mNIS+7$_{Ionis}$ between inotersen and placebo was −19.73 points (95% CI, −26.43 to −13.03; statistically significant in favour of inotersen). In a sensitivity analysis that included all randomized patients and conservatively imputed missing data, the LSM difference in change from baseline remained statistically significant in favour of inotersen (−14.89 points; 95% CI, −22.55 to −7.22).

All other outcomes, including cardiovascular assessments, were analyzed statistically outside of the hierarchy testing procedure and differences between groups for these outcomes are difficult to interpret. [redacted] For PND score, most patients experienced no change from baseline (65% inotersen and 71% placebo). [redacted]

Harms (Safety)

In NEURO-TTR, more patients who received inotersen discontinued treatment due to an AE than patients who received placebo (14% versus 3%). More patients who received inotersen also had an SAE (32% versus 22%).

Of the AEs of special interest, ocular AEs potentially related to vitamin A deficiency occurred in approximately an equal proportion of patients receiving placebo or inotersen (20% versus 21%). More patients receiving inotersen had renal impairment (21% versus 10%), including two patients who experienced serious glomerulonephritis (zero placebo patients), and thrombocytopenia (13% versus 2%).

Five deaths occurred in the inotersen group and none in the placebo group. Four of the deaths were attributed to disease progression or complication and one death was due to intracranial hemorrhage in association with a platelet count of approximately 10×10^9/L, possibly associated with inotersen treatment.

Cost and Cost-Effectiveness

Inotersen is a single-dose pre-filled syringe, administered as a subcutaneous injection at a dosage of 300 mg weekly. At the manufacturer's submitted price of $8,077 per pre-filled syringe, the average annual drug cost is approximately $420,000 per patient.

The manufacturer submitted a cost-utility analysis from the perspective of a Canadian publicly funded health care payer comparing inotersen with BSC for the treatment of stage I or stage II polyneuropathy in patients with hATTR during a lifetime time horizon. A Markov model with health states defined by the three Coutinho disease stages based on ambulatory status and death was used to model disease progression. Patients entered the model in stage I or stage II according to the baseline trial characteristics observed in NEURO-TTR and were assumed to discontinue treatment upon entering stage III. Transition probabilities were derived from the NEURO-TTR trial by mapping Norfolk Total Quality of Life (TQoL) values to Coutinho disease stages. Utility values were obtained from a Brazilian utility study of hATTR patients, converted to a Canadian value set and were time dependent, increasing (or decreasing) for each cycle patients remained in the same health state on inotersen (or BSC). Health state costs were estimated by interviews with Canadian clinicians, and were treatment-specific, such that within the same health state, patients receiving inotersen would have a 43% reduction in health state costs compared with patients receiving BSC.

CADTH identified several key limitations with the manufacturer's economic submission:

- The validity of the technique to map Norfolk TQoL scores to Coutinho stages were uncertain.
- The health states used in the model did not capture all aspects of the condition, which led the manufacturer to apply treatment-specific utility values and health state costs.
- Treatment costs were underestimated. The model factored inotersen compliance and assumed patients would discontinue treatment upon entering stage III, which would be inconsistent with clinical practice.
- The impact to caregivers was not appropriate for the public-payer perspective.
- Uncertain methods were taken to convert utilities into a Canadian utility value set, resulting in utility values that lacked face validity.
- The assumptions used to extrapolate treatment benefit were more favourable for inotersen.
- The mortality rates used were based on polyneuropathy stage despite the leading causes of death being cardiac related.
- A fixed standard error was used for most parameters, such that results may not reflect true parameter uncertainty.

CADTH reanalyses accounted for some of the identified limitations: assuming no difference in treatment-specific utilities or health state costs; having patients continue inotersen treatment after progressing to stage III; removing caregiver disutility; using the original utility values elicited on Brazilian patients with the Brazilian preference set; assuming treatment efficacy beyond the trial period to reflect the week 35 to week 66 data in the NEURO-TTR trial for both inotersen and BSC; using survival curves from the published literature to estimate mortality; increasing inotersen compliance to 100%; and, using standard deviations where available to more accurately represent parameter uncertainty. This resulted in a revised ICUR for inotersen of $1,322,377 per QALYs gained compared with BSC. To be considered cost-effective at a willingness-to-pay threshold of $50,000 per QALYs, an 88% reduction in price would be required.

CADTH was unable to address several key limitations to the manufacturer's model, including uncertainties associated with the model structure and the validity in modelling disease progression based on mapping the trial-reported Norfolk TQoL score to Coutinho stages.

July 17, 2019 Meeting (Initial)

CDEC Members

Dr. James Silvius (Chair), Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Dr. Peter Jamieson, Mr. Allen Lefebvre, Ms. Heather Neville, Dr. Rakesh Patel, Dr. Emily Reynen, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

Regrets

None

Conflicts of Interest

None

November 20, 2019 Meeting (Reconsideration)

CDEC Members

Dr. James Silvius (Chair), Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Mr. Allen Lefebvre, Ms. Heather Neville, Dr. Rakesh Patel, Dr. Danyaal Raza, Dr. Emily Reynen, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

Regrets

One CDEC member.

Conflicts of Interest

None

December 11, 2019 Meeting

CDEC Members

Dr. James Silvius (Chair), Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Mr. Allen Lefebvre, Ms. Heather Neville, Dr. Rakesh Patel, Dr. Danyaal Raza, Dr. Emily Reynen, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

Regrets

None

Conflicts of Interest

None