CADTH

CADTH COMMON DRUG REVIEW

Pharmacoeconomic Review Report

INOTERSEN (TEGSEDI)

(Akcea Therapeutics, Inc.)

Indication: Stage I or II polyneuropathy in adults with hereditary transthyretin-mediated amyloidosis (hATTR)

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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.

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

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Abbreviations

AE	adverse event
BSC	best supportive care
eGFR	estimated glomerular filtration rate
EQ-5D	EuroQol 5-Dimensions questionnaire
EQ-5D-3L	EuroQol 5-Dimensions 3-Levels questionnaire
HAC	Hereditary Amyloidosis Canada
hATTR	hereditary transthyretin-mediated amyloidosis
ICUR	incremental cost-utility ratio
PND	polyneuropathy disability
QALY	quality-adjusted life-year
THAOS	Transthyretin Amyloidosis Outcomes Survey
TQoL	total quality of life
UPCR	urine protein to creatinine ratio

Table 1: Summary of the Manufacturer's Economic Submission

Drug Product	Inotersen (Tegsedi)
Study Question	From the perspective of the publicly funded health care payer, what is the incremental cost-effectiveness of inotersen compared with best supportive care in adult patients with hereditary transthyretin-mediated amyloidosis (hATTR) with stage I or II polyneuropathy in Canada?
Type of Economic Evaluation	Cost-utility analysis
Target Population	Stage I or stage II polyneuropathy in adult patients with hATTR
Treatment	Inotersen, administered by pre-filled syringe (284 mg dose in 1.5 mL), injected subcutaneously every week
Outcome	QALYs
Comparator	BSC consisting of supportive care medication
Perspective	Canadian publicly funded health care payer
Time Horizon	Lifetime (41 years)
Results for Base Case	Inotersen was more costly ($1,064,922) and more effective (2.03 QALYs) than BSC with an ICUR of $523,448 per QALY gained.
Key Limitations	CDR identified several key limitations with the submitted analysis: • Disease progression was described in the manufacturer's model based on Coutinho's classification. To model disease progression and treatment efficacy, the manufacturer mapped the Norfolk total quality-of-life scores observed in the NEURO-TTR trial to Coutinho stage. The validity of this approach is uncertain and CADTH could not assess the impact of this limitation. • Health states in the model do not capture all the important aspects of the condition and, therefore, the manufacturer applied treatment-specific utilities and health-state costs. • The manufacturer assumed that patients would discontinue treatment when they entered Coutinho stage III. According to clinical experts consulted by CADTH, given the limited treatments, treatment discontinuation is unlikely as the condition worsens. If patients in Coutinho stage III remain treated, this would increase the drug costs for inotersen. • Impact on caregiver (in terms of disutilities) should not be included in a public payer perspective. • Approach taken to convert Brazilian utility values to Canadian values had limited validity. • Optimistic assumptions were made to extrapolate treatment effects for inotersen compared with BSC. • Different mortality effects by Coutinho stage were assumed. According to clinical experts consulted by CADTH, although an increased mortality is expected in patients with hATTR, it is unlikely related to Coutinho stages, given that the leading causes of death are cardiac-related.

CDR Estimate(s)	The CADTH base-case reanalysis adjusted the utilities inputs with the removal of treatment-specific utilities and caregivers disutilities, and the direct application of the Brazilian utility values; revised costs inputs with the removal of treatment-specific health-state costs and the adjustment of treatment costs; assumed an increased mortality risk that was applied irrespective of Coutinho stage; and extrapolated treatment effects based on the week 35 to 66 outcomes reported in the NEURO-TTR trial. • Based on these revisions, CADTH found that the ICUR of inotersen compared with BSC was $1,322,377 per QALY gained. • A price reduction of at least 88% would be required for inotersen to be considered cost-effective at a $50,000 per QALY threshold. • CADTH was unable to address several key limitations, including uncertainties associated with the model structure and the validity in modelling disease progression based on mapping the trial-reported Norfolk total quality-of-life score to Coutinho stages.

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	Inotersen (Tegsedi)
Indication	Stage I or II polyneuropathy in adults with hereditary transthyretin-mediated amyloidosis (hATTR)
Listing Request	As per indication
Dosage Form(s)	Subcutaneous injection
NOC Date	October 3, 2018
Manufacturer	Akcea Therapeutics, Inc.

Executive Summary

Background

Inotersen (Tegsedi) is indicated for adults with hereditary transthyretin-mediated amyloidosis (hATTR) with stage I or stage II polyneuropathy.[1] Inotersen is administered through subcutaneous injection at a dose of 284 mg (300 mg inotersen sodium)/1.5 mL once every week using a single-dose pre-filled syringe.[1] Oral supplementation with the recommended daily allowance of vitamin A (3,000 IU vitamin A per day) should be continued while on treatment alongside regular monitoring of platelet counts to inform dose adjustments. The recommended frequency of monitoring varies according to platelet count levels, ranging from daily to every two weeks.[1] The price of inotersen is $8,076.92 per pre-filled syringe,[2] which results in an annual cost of approximately $420,000.

The manufacturer submitted a cost-utility analysis comparing inotersen with best supportive care (BSC). BSC was defined as management of symptoms and support of function of failing organs. The analysis was conducted from the perspective of the Canadian publicly funded health care payer over a lifetime time horizon (41 years) with cycles defined as every four weeks. Future costs and benefits were discounted at 1.5%.[2] A Markov model was developed with patients transitioning through three health stages based on ambulatory status and an absorbing death state. Patients in Coutinho stage I or II begin inotersen according to the baseline characteristics reported in the NEURO-TTR and were assumed to discontinue treatment upon reaching stage III.[2] The clinical efficacy data used in the model came from the NEURO-TTR study by mapping Norfolk total quality-of-life (TQoL) values to the Coutinho disease stages. Utilities for each health state were found in the literature and converted in an attempt to represent Canadian health state preferences. Health-state utilities were further adjusted by treatment-specific time-dependent utilities based on a regression analysis of the Norfolk TQoL score reported in NEURO-TTR mapped to the EuroQol 5-Dimensions health status questionnaire (EQ-5D).[2] Health-state costs were estimated based on interviews with Canadian clinicians. No treatment costs were assumed in patients on BSC; rather, the manufacturer assumed that patients who were on or had discontinued inotersen would have a 43% reduction in health-state costs across all Coutinho disease stages to reflect the reduction in health care resource use expected in patients with current or past exposure to inotersen.[2]

The manufacturer reported that inotersen was $1,064,922 more costly than BSC and more effective, with 2.03 additional QALYs, resulting in an incremental cost-utility ratio (ICUR) of $523,448 per QALY gained.[2] In this analysis, inotersen had a 0% probability of being the most likely cost-effective intervention at any willingness-to-pay threshold below $400,000 per QALY gained.[2]

Summary of Identified Limitations and Key Results

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

In particular, there were a number of limitations associated with the model conceptualization. Progression of polyneuropathy in the manufacturer's model was based on Coutinho stages, a functional scale that measures ambulatory ability.[3] As Coutinho stages were not measured in the NEURO-TTR study,[4,5] Norfolk TQoL was used to estimate transitions between Coutinho stages based on defining Norfolk TQoL cut-offs for each Coutinho stage.[6] However, considerable heterogeneity has been reported between Norfolk TQoL scores over Coutinho stages, and uncertainty remains regarding the optimal cut-off definition.[7] Furthermore, patients with hATTR will often present, to varying degrees, neuropathy, cardiomyopathy, vitreous opacities, kidney disease, and meningeal involvement.[8] The manufacturer's model only considered neuropathy explicitly with their selected health states and did not capture other important elements of the condition. In an attempt to account for these differences within health states, the manufacturer applied utility values and health-state costs that differed by treatment,[6] which is contrary to CADTH guidelines[9] and reduces model transparency. The manufacturer also assumed different mortality effects by Coutinho stage.[6] However, clinical experts consulted by CADTH have stated that although there is likely an increased risk of mortality in patients with this condition, polyneuropathy itself is unlikely to be a primary cause of mortality. Rather, the cardiac effects are quite profound and patient mortality is often related to cardiac manifestations of the disease.

The manufacturer also made some optimistic assumptions in favour of inotersen. In the manufacturer's analysis, it was assumed that patients who progress to stage III (i.e., patients who become bedridden or confined to a wheelchair) will stop inotersen and continue on BSC.[6] According to clinical experts, there is a reluctance in clinical practice to discontinue a patient's existing treatment solely because they require wheelchair assistance. It was also assumed that costs on inotersen would be 10% lower to reflect the difference in dose received compared with the expected dose that was reported in the NEURO-TTR trial.[6] However, given that this is a self-administered medication, it is uncertain how many patients would not fill their prescriptions. Assumptions about the long-term benefits of inotersen were also optimistic compared with the assumptions for BSC. The manufacturer assumed that, beyond week 66, patients on inotersen would have the same benefit observed between weeks 35 and 66, whereas for BSC, it was assumed that patients could not improve after week 66.[6] Caregiver disutilities were also applied,[6] which should not be included, given the chosen perspective of the analysis.

There were further limitations relating to the modelling methods used. Arbitrary levels of uncertainty were used in the probabilistic analysis and the methods used to convert Brazilian utility values to reflect Canadian health-state preferences were not appropriate.

CADTH attempted to address the above limitations by: using the same utility values and costs for health states; eliminating the disutility associated with the impact on caregivers; assuming all prescriptions are filled; maintaining inotersen treatment for patients in stage III; using Brazilian utility values;[10] assuming an increased mortality risk that was not specific to Coutinho stage;[11] using 35- to 66-week data to extrapolate efficacy beyond week 66 for both inotersen and BSC; and using the reported standard deviations, where possible, to define probability distributions. CADTH was unable to address the uncertainty associated with describing disease progression based on Norfolk TQoL.

Based on the CADTH reanalyses, BSC had lower expected lifetime costs ($255,497) and QALYs (2.19) compared with inotersen, which would cost $1,318,508 for 2.99 QALYs. This resulted in inotersen having an ICUR of $1,322,377 per additional QALY compared with BSC.

Conclusions

A number of key limitations identified in the manufacturer's model had a large impact on the interpretation of the cost-effectiveness of inotersen. CADTH was unable to address several key limitations, including uncertainties associated with the model structure and the validity in mapping Norfolk TQoL score to Coutinho stage.

Based on the reanalyses that were possible, CADTH's findings were aligned with the manufacturer's: inotersen is not a cost-effective option at a cost-effectiveness threshold of $50,000 per QALY. In adults with hATTR stage I or II polyneuropathy, the CADTH reanalysis estimated the ICUR for inotersen to be $1,322,377 per additional QALY compared with BSC. A price reduction of at least 88% would be required for the ICUR for inotersen to fall below the $50,000 per QALY threshold compared with BSC.

Alternative treatments may be available to patients with this condition; some of these treatments are available through special access (e.g., tafamidis), while others are currently under review by Health Canada (e.g., patisiran). No evidence is available regarding the cost-effectiveness of inotersen compared with these other drugs.

Information on the Pharmacoeconomic Submission

Summary of the Manufacturer's Pharmacoeconomic Submission

The manufacturer submitted a cost-utility analysis comparing inotersen with best supportive care (BSC) in adult patients with hereditary transthyretin-mediated amyloidosis (hATTR) with stage I or II polyneuropathy.[6] BSC was defined as the management of symptoms and the support of function of failing organs.[6] The model used a lifetime horizon (41 years) from the perspective of a publicly funded health care payer with costs and clinical outcomes (quality-adjusted life-years [QALYs]) discounted at 1.5% per annum.[6] The model reflected a population that had baseline characteristics as reported in the NEURO-TTR trial (68.60% male; average age, 59; 65.7% in stage I and 34.3% in stage II).[6]

Model Structure

A Markov model was submitted by the manufacturer with three living health states measuring hATTR disease progression and an absorbing death state.[6]

To characterize the progression of polyneuropathy, Coutinho's classification was used to define the health states:

- stage I, patients do not require any assistance with ambulation
- stage II, patient do require assistance with ambulation (excluding wheelchair)
- stage III, patients need a wheelchair or are bedridden.[3]

The model allowed patients to remain stable (i.e., continue in the same health state), deteriorate (i.e., progress from stage I to stage II or stage III; progress from stage II to stage III) or improve (i.e., only patients in stage II can transition to stage I) (Figure 1). Patients in all stages could die and transition to death, the absorbing health state.[6] Transition probabilities were estimated from the NEURO-TTR study,[4,5] using the Norfolk total quality-of-life (TQoL) score.[6] Cut-off scores for the Norfolk TQoL were mapped onto the Coutinho disease stages based on the Transthyretin Amyloidosis Outcomes Survey (THAOS) from a UK Evidence Review Group report on tafamidis, a transthyretin stabilizer.[7] Two sets of transition probabilities were estimated using data from week 0 to week 35 and from week 35 to week 66 of the NEURO-TTR trial.[4,5] To extrapolate transitions beyond 66 weeks, the manufacturer's model assumed the transitions would remain identical to the transitions observed from week 35 to 66; this was further adjusted for BSC given the manufacturer's assumption that patients on BSC could not improve.[6] Hazard ratios sourced from the literature[12] were applied to account for the increased risk of mortality in patients with hATTR, stratified by Coutinho stage, compared with Canadian general-population mortality.[6] Treatment duration for inotersen was estimated using data from the NEURO-TTR trial and its extension study[4,5] and extrapolated using an exponential distribution.[6] The manufacturer further assumed that treatment with inotersen would be discontinued when patients reach stage III.[6]

Utilities for each health state came from a study of the THAOS registry.[10] This publication reported utilities for 93 Brazilian patients with polyneuropathy and hATTR and the manufacturer converted the utilities reported in this publication to a Canadian value set.[6] Utility values were time-dependent, increasing for each cycle where patients on inotersen

remained in the same health state and decreasing for each cycle where patients on BSC remained in the same health state. This was based on the observed difference in the Norfolk TQoL score from baseline to the end of the NEURO-TTR trial and converted to a EuroQol 5-Dimensions questionnaire (EQ-5D) score using an algorithm from Faria et al. (2012).[7] A decrement in utility was also applied to capture the caregivers' burden associated with the disease. Disutilities due to adverse events (AEs) were also included.[6] The model included drug-related costs (acquisition, administration, and monitoring costs), medical costs relating to health states, and AE management costs.[6] Drug costs for inotersen were provided by the manufacturer; the costs of BSC were assumed to be captured within the health-state costs. The frequency of health care resource use relating to each health state was informed by interviews with Canadian clinicians.[6] The manufacturer assumed that, within the same health state, patients on inotersen would have a 43% reduction in health-state costs compared with patients on BSC. For patients who discontinue, it was assumed there would be no treatment cost and that they would maintain the 43% reduction in health state costs, while their disease progression would reflect that of patients on BSC.[6] The cost of inotersen was further adjusted to be 90% of the recommended prescription costs to match the actual dose that was administered in the NEURO-TTR trial.[5]

Manufacturer's Base Case

Inotersen was found by the manufacturer to be $1,064,922 more expensive than BSC and the estimated benefit of inotersen was an additional 2.03 QALYs compared with BSC, resulting in an incremental cost-utility ratio (ICUR) for inotersen of $523,448 per QALY gained compared with BSC.[6] Table 2 shows the contribution of the different sources of costs to the overall total incremental cost. The active treatment made the largest contribution with a lifetime (41 years) incremental cost of $1,165,042. The largest cost saving attributed to inotersen was that of health care resource utilization, with an expected saving of $100,772.

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

	Inotersen (a)	BSC (b)	Difference (a Minus b)
QALYs	2.34	0.31	2.03
LYs	12.19	10.91	1.28
[a]Active treatment	$1,165,042	$0	$1,165,042
[a]Administration	$0	$0	$0
[a]Treatment monitoring	$362	$0	$362
[a]Adverse events	$1,937	$854	$1,083
[a]Health care resource utilization	$342,509	$443,280	−$100,772
[a]One-off transition costs	$6,092	$6,886	−$794
Total costs	$1,515,942	$451,021	$1,064,922
$/QALY			$523,448

BSC = best supportive care; LY = life-year; QALY = quality-adjusted life-year.

[a] Reported in the manufacturer model.

Source: Manufacturer pharmacoeconomic submission.[6]

Summary of Manufacturer's Sensitivity Analyses

Uncertainty was addressed by scenario analyses.[6] The manufacturer tested scenarios such as the following:

- assuming no limits on BSC transitions i.e., that patients on BSC could improve from stage II to stage I after 66 weeks
- assuming that additional mortality risk associated with hATTR is not stratified by Coutinho stage
- alternative parametric distributions for treatment discontinuation
- varying treatment compliance rates
- including phlebotomist costs
- excluding the effects of AEs both in terms of costs and disutility
- assuming different reductions of health care costs due to inotersen
- revising the source informing health care resource use to UK resources
- including liver transplantation costs
- applying different discount rates
- assuming only one caregiver is impacted for each disease stage
- removing treatment-specific utilities
- setting different time horizons.

All of the manufacturer's scenario analyses comparing inotersen with BSC resulted in inotersen having an ICUR greater than $400,000 per QALY gained.[6] The scenarios with the largest decrease in the ICUR were the scenarios assuming that a proportion of patients in stage I or II would ultimately have a liver transplant (10%: $445,926 per QALY; 50%: $451,586 per QALY) and setting the compliance rate to be lower (80%: $459,919 per QALY). The scenarios with the largest increase in the ICUR were the scenarios assuming a generalized gamma function for discontinuation ($621,755 per QALY) and the scenario where there were no mortality differences between Coutinho stages ($590,408 per QALY).[6]

Limitations of Manufacturer's Submission

1. **Disease severity and progression measured by Norfolk TQoL scores.** As the NEURO-TTR study did not include Coutinho stage as a trial outcome,[4,5] the Norfolk TQoL collected in the study was used to estimate transitions between Coutinho stages and, therefore, measure changes within the health states. Specifically, Norfolk TQoL cut-offs were defined in order to map the observed patient-level Norfolk TQoL values from the NEURO-TTR study to the proportion of patients in each Coutinho stage.[6] As the clinical review noted, Norfolk TQoL is a valid measure of hATTR severity and is able to discriminate between patients with and without disease and between patients with different stages of the disease.[13] However, the rationale for the Norfolk TQoL cut-offs that were chosen by the manufacturer to assess disease progression was not well defined. Previous reviews on the use of Norfolk TQoL scores to model the progression of hATTR have questioned this approach, given the heterogeneity in Norfolk TQoL scores over the Coutinho stages.[7] Given that the definition of the cut-off will impact the sensitivity and specificity of the scale in terms of the proportion of patients in each Coutinho stage, there is high uncertainty regarding the robustness of the economic

results to the cut-off selected. The effect of measuring transitions using a measure other than TQoL or using different cut-offs of TQoL have not been discussed by the manufacturer.

A related concern regarding how the clinical data were incorporated into the economic model relates to the differences in the time periods. The NEURO-TTR trial assessed clinical outcomes at two time points (i.e., week 35 and at week 65 or 66),[4,5] whereas the model's cycle length was set to every four weeks.[6] Linearity was assumed in order to convert the six-month transition probabilities from the trial to monthly transition probabilities for the economic evaluation.[6] This approach led to inputs that are unlikely to accurately reflect disease progression. According to the clinical experts consulted for this review, it is unlikely for a patient's disease to progress from stage I to stage III within a four-week time period and yet, in the manufacturer's model, a small portion of patients on BSC could deteriorate from Coutinho stage I to stage III.

Given these concerns, the cost-effectiveness results are uncertain and CADTH could not address these limitations.

2. **The health states used in the model did not capture all aspects of the condition or its treatment**. To describe disease progression, health states in the model were defined by Coutinho stages. Coutinho stages were developed using a population of patients with the V30M mutation and their applicability in a non-V30M population is unknown.[14] Coutinho stages are based on mobility and polyneuropathy impairment only and do not capture autonomic symptoms associated with hATTR amyloidosis. hATTR is a multi-faceted heterogeneous disease that causes motor, sensory, and autonomic neuropathy that leads to progressive muscle weakness and disability, pain, wasting, gastrointestinal symptoms, and other autonomic symptoms, such as orthostatic hypotension.[3,14] To compensate for the inability of the model to capture all health changes through its health states, the manufacturer applied treatment-specific utility values and health state costs.[6]

   The manufacturer stated that a patient-level analysis demonstrated that patients' TQoL improved while on inotersen and reduced while on BSC from baseline to week 66. Given this observation, they concluded that patients on inotersen would improve the longer these patients were in the same health state and that patients on BSC would worsen the longer they remained in the same health state.[6] The need to change the utility, by treatment and by duration, within a health state demonstrates the inability of the health state to adequately capture the important differences in health that would be expected with the condition and its treatment. The use of treatment-specific utility values is contradictory to CADTH guidelines that recommend that utilities should be associated with health states.[9] To implement this in the manufacturer's model, the relative change in TQoL per cycle (i.e., the difference in TQoL at baseline compared with the end of the NEURO-TTR study at 66 weeks) was converted into an EQ-5D utility score using the algorithm proposed by Faria et al.[7] The utility for patients on inotersen was therefore increased by 0.0002 for each cycle that they remained in the same health state and the utility for patients on BSC was reduced by 0.0038 for each cycle that they remained in the same health state.[6] In the case of this review, this led to some cycles in which stage II patients on inotersen had higher quality of life than stage I patients on BSC. This approach is further inappropriate because, in effect, it double counts the treatment benefits of inotersen, given that changes in Norfolk TQoL informed both the health-state transitions and the additional treatment-specific utilities. Together, this approach favours inotersen by producing higher expected QALYs for inotersen, thus reducing the ICUR for inotersen.

Rather than calculating the treatment costs associated with BSC, the manufacturer assumed that patients who were on or who had discontinued inotersen would have a 43% reduction in health-state costs across all Coutinho disease stages.[6] This reduction reflected the manufacturer's assumption that patients with existing or past exposure to inotersen would require less supportive medication and/or medical care. However, this value was taken from an assessment of patisiran by the National Institute of Health and Care Excellence in the UK that applied a Delphi process with UK clinicians.[15] There are several issues with this approach. There is no reason to expect that two different drugs with different clinical effects would have the same effect on health care resource use. It is further unclear how generalizable the UK health care system is compared with Canada's. The clinical experts consulted by CADTH noted differences in treatment practices and the management of patients with hATTR between the two countries. Furthermore, taking costs from the UK's perspective would have incorporated social services costs into its calculation, which would not be relevant to the Canadian public health care payer's perspective. If the cost reduction was due to differences in social spending rather than medical spending, this value may be overestimated. It is also unclear why patients who had discontinued inotersen would continue to have a 43% reduction applied to the health-state costs, since these patients would have transitioned to be managed by BSC. 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 inputs in the manufacturer's model. However, setting treatment-related costs for BSC to zero and assuming a crude 43% reduction in health-state costs is unlikely to capture the true costs associated with BSC across the different stages of the condition and reduces the overall transparency of the economic model. Furthermore, as noted, this approach, in which both patients who were on or who have discontinued inotersen have a reduction in health-state costs, would favour inotersen by producing lower expected costs and a lower ICUR. In the CADTH reanalysis, treatment-specific utilities and a reduction in health care resource use was not included.

3. **Patients discontinue treatment upon entering stage III.** In the manufacturer's analysis, it was assumed that patients who progress to stage III (i.e., patients who become confined to a wheelchair or bedridden) will stop inotersen and continue on BSC.[6] This results in patients in stage III having no costs or clinical benefits associated with inotersen. According to clinical experts consulted by CADTH for this review, there is reluctance in clinical practice to discontinue a patient's existing treatment solely because they require wheelchair assistance, given that there are limited alternative treatment options and the decision to use a wheelchair is subjective and often patient-related (e.g., patient's fear of falling). Experts noted that safety concerns and perverse incentives are associated with this stopping rule, such that patients may not use appropriate ambulation devices in order to continue receiving inotersen treatment. Furthermore, the clinical experts noted that patients who require a wheelchair may have residual motor or sensory function in their upper limbs that may benefit from treatment with inotersen. In the CADTH reference case, it was assumed that patients would continue to be treated with inotersen even upon reaching stage III. A scenario analysis was further conducted that adopted the manufacturer's assumption that patients would discontinue treatment upon entering stage III.
4. **Caregiver impacts incorporated into the base case are not appropriate for the public payer perspective.** Caregiver disutility was applied within the manufacturer's base case to patients in all health states. It was assumed that, for patients in Coutinho stages I and II, one caregiver would be affected, while patients in Coutinho stage III

would have two affected caregivers.[6] The inclusion of caregiver disutilities would not be applicable within the public payer perspective but would be suitable under a societal perspective. Inclusion of caregiver disutilities would favour inotersen, as patients on inotersen progressed more slowly to Coutinho stage III and would therefore have fewer reductions in QALYs due to caregiver impacts compared with patients on BSC.

5. **Methods for converting Canadian utility value set.** The health states utilities used in the manufacturer's model were based on a publication of 93 Brazilian patients (stage I: n = 55, stage II: n = 15, and stage III: n = 8) elicited by the EuroQol 5-Dimensions 3-Levels questionnaire (EQ-5D-3L).[10] The original utilities were reported using Brazilian preferences for EQ-5D health states. The manufacturer converted these utilities by matching the average utilities to the closest EQ-5D-3L profiles reported based on the Brazilian preference set. Canadian preference weights[16] were then applied to these EQ-5D profiles to estimate Canadian utility values. However, the average utilities estimated for the Brazilian population would be an average of several different EQ-5D profiles and it is possible that none of the patients reported the profiles closest to the average. Matching the utilities to the closest EQ-5D-3L profiles further limits face validity. Specifically, EQ-5D-3L is a generic multi-attribute utility instrument that describes a health state based on five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, and each dimension can be marked on three levels (no problems, some problems, extreme problems).[17] Comparing the description for the EQ-5D profile for stage II (EQ-5D profile 22213) and stage III (EQ-5D profiles 33311 and 31332) suggests that patients in stage III have improvements in anxiety/depression (as the score reduces from 3 to either 1 or 2) and potential improvement in terms of self-care (as the score reduces from 2 to 1) when compared with patients in stage II. This would not be expected, according to clinical experts consulted on this review.
6. **Assumptions for extrapolating treatment benefits were more favourable for patients on inotersen**. The transition probabilities for inotersen used in the manufacturer's model after 66 weeks were the same as those calculated from the 35- to 66-week data in the NEURO-TTR study.[6] The transition probabilities for BSC used in the model after 66 weeks were also calculated from the 35- to 66-week data; however, it was further assumed that, after 66 weeks, patients on BSC would not transition from stage II to stage I, despite the evidence from the 35- to 66-week trial data, which showed 2.61% of patients improving from stage II to stage I during the last 31 weeks of the study.[6] Assuming that patients on inotersen continue to improve after 66 weeks, but not patients receiving BSC, is inappropriate and not reflective of the available data. This assumption favours inotersen. In the CADTH reanalysis, both treatments were assumed to transition in the extrapolation period in the same manner as the 35- to 66-week data.

   Furthermore, week 35 to 66 results represented the most optimistic changes in terms of disease progression.[5] Given the uncertainty in the long-term effects of treatment, scenario analyses were conducted that applied different assumptions to test the sensitivity of the model against alternative scenarios of long-term treatment effects.
7. **Different mortality effects by Coutinho stage**. In the manufacturer's analysis, mortality was assumed to be higher for patients in more progressed Coutinho stages. Mortality hazard ratios were estimated based on another system of classification, the polyneuropathy disability score (PND), which categorizes polyneuropathy severity into four stages.[12] Hazard ratios based on each level of the PND scale were then converted into hazard ratios for the three Coutinho stages.[6] These hazard ratios were not further

based on the age of the patient or the time with disease. This approach is not valid, considering the clinical condition. According to the clinical experts consulted by CADTH for this review, although there is likely an increased risk of mortality in patients with this condition, polyneuropathy itself is unlikely to be a primary cause of mortality. Rather, the cardiac effects are quite profound and patient mortality is often related to cardiac manifestations of the disease. In the CADTH reanalysis, it was assumed there would be no mortality differences between Coutinho stages and, instead, mortality was extrapolated from a study by Sattianayagam et al.[11]

8. **Reduction in costs due to lower compliance.** In the NEURO-TTR study, patients were reported to consume 90% of their treatment doses.[5] Therefore, in the manufacturer's model, the cost of inotersen was decreased by 10% to capture the effects on the cost of treatment due to the expected lack of compliance.[6] However, given that inotersen is self-administered, prescriptions may continue to be filled even if patients are not compliant with treatment. Assuming compliance is lowered for inotersen would reduce the expected treatment costs, favouring inotersen. Furthermore, it is unclear how the effects of compliance may impact treatment efficacy, as efficacy inputs in the model were based only on a subset of all patients who received at least one dose of treatment. In NEURO-TTR, 113 patients on inotersen and 60 patients on BSC were reported to have received one dose of treatment, whereas, in the manufacturer's model, the efficacy data at week 0 to 35 and week 35 to 66 were based only on patients for which TQoL data were available for 88 and 76 patients, respectively, for inotersen, and 50 and 44 patients, respectively, for BSC.[6] In the CADTH reanalysis, it was assumed that patients would continue to fill their prescriptions in order to provide a more conservative estimate.
9. **Use of an arbitrary coefficient of variation**. For the majority of costs, utilities, and probability parameters within the manufacturer's model, the standard error was fixed to be 5% of the mean estimates. The uncertainty observed in the probabilistic results may therefore not fully reflect the true uncertainty around model parameters. The arbitrary assumption in defining probability distributions is inappropriate,[9] as parameters with low sensitivity but higher uncertainty should impact the model's output more than more sensitive parameters that are estimated more precisely.

CADTH Common Drug Review Reanalyses

CADTH conducted the following reanalyses to address the key limitations described above:

1. removal of treatment-specific utilities
2. removal of a treatment-specific reduction in health care resource use
3. patients continue treatment on inotersen even after advancing to stage III; given the lack of data on the efficacy of inotersen in stage III polyneuropathy patients, CADTH assumed that patients could not improve upon reaching stage III
4. removal of caregiver disutilities
5. selection of the original utility values elicited on Brazilian patients with the Brazilian preference set for CADTH's base-case reanalysis, given the limited utility data available on this condition;[10] although Brazilians may have different utility weights than Canadians, there was insufficient data to adequately convert the Brazilian values to a Canadian preference set
6. treatment efficacy beyond the observed trial period reflects the week 35 to 66 data in the NEURO-TTR study for both the inotersen and BSC groups[4,5]

7. Kaplan Meier curves on survival were digitalized from Sattianayagam et al. 2012[11] and the models with the best statistical fit was selected separately for patients with V30M mutation (Weibull) and with T60A mutation (log-logistic) ; mortality was weighted, assuming 51.7% of patients have the V30M mutation[5] and the rest have non-V30M (i.e., T60A) mutations
8. patients are fully compliant with inotersen treatment
9. applied available standard deviations for the utility values when conducting the probabilistic analysis; uncertainty is likely underestimated in this model, given the arbitrary nature to which parameter distributions were defined in the probabilistic analysis.

All comparisons were between inotersen and BSC. The CADTH reanalysis demonstrates that each individual change to the model had a small effect on the overall ICUR, with the removal of caregiver utility having the largest effect, increasing the ICUR of inotersen compared with BSC to $628,530 per additional QALY. Most changes increased the ICUR, although increasing the probability of patients improving on BSC using the week 35 to 66 data increased the QALYs of both inotersen and BSC patients and resulted in a lower ICUR of $490,606 per additional QALY (Table 3).

Compared with the manufacturer's results, the CADTH reanalysis, which incorporated all changes to address the key limitations noted by CADTH, estimated higher expected QALYs for both BSC and inotersen, although expected costs were lower for BSC and higher for inotersen. In the CADTH reanalysis, the ICUR for inotersen was $1,322,377 per additional QALY compared with BSC (Table 3).

Table 3: CADTH Common Drug Review Reanalysis of Limitations

	Scenario	Treatments	QALYs	Cost ($)	Cost per QALY ($)
	Base case submitted by manufacturer	BSC	0.31	451,021	
		Inotersen	2.34	1,515,942	523,448
1	No change of utilities within a health state	BSC	0.98	450,662	
		Inotersen	2.85	1,515,545	568,218
2	No difference in health-state costs	BSC	0.31	450,960	
		Inotersen	2.35	1,524,184	527,925
3	Patients do not discontinue treatment upon entering stage III	BSC	0.31	450,735	
		Inotersen	2.35	1,580,963	554,041
4	No reduction in costs due to compliance	BSC	0.31	450,187	
		Inotersen	2.34	1,645,162	587,741
5	No disutility to caregivers	BSC	1.95	450,273	
		Inotersen	3.65	1,515,933	628,530
6	Brazilian HRQoL preferences	BSC	0.31	450,318	
		Inotersen	2.35	1,516,025	524,207
7	No difference in mortality between Coutinho stages	BSC	0.62	287,778	
		Inotersen	2.08	1,163,010	597,730
8	Extrapolate BSC using week 35 to 66 data	BSC	0.88	417,433	
		Inotersen	3.05	1,482,811	490,606
9	Use standard deviations for utilities	BSC	0.31	451,076	

	Scenario	Treatments	QALYs	Cost ($)	Cost per QALY ($)
		Inotersen	2.34	1,515,274	523,426
	CADTH reference (1 + 2 + 3 + 4 + 5 + 6 + 7 + 8 + 9)	BSC	2.19	255,497	
		Inotersen	2.99	1,318,508	1,322,377

BSC = best supportive care; HRQoL = health-related quality of life; QALY = quality-adjusted life-year.

The scenario analyses undertaken on the CADTH reference case resulted in ICURs that were all greater than $1,200,000 per additional QALY (Table 14).

Price-reduction analyses on the CADTH base case found that, in order for inotersen to be considered cost-effective at a willingness-to-pay threshold of $50,000 per QALY, an 88% reduction in price would be required (Table 4).

Table 4: CADTH Common Drug Review Reanalysis Price-Reduction Scenarios

ICURs of Inotersen Versus Best Supportive Care		
Price	**Base-Case Analysis Submitted by Manufacturer ($)**	**Reanalysis by CDR ($)**
Submitted	602,538	1,322,377
10% reduction	466,466	1,149,490
20% reduction	409,275	1,001,848
30% reduction	351,978	864,421
40% reduction	294,673	725,271
50% reduction	237,764	581,432
60% reduction	179,915	440,933
70% reduction	122,906	298,642
80% reduction	65,869	160,841
90% reduction	8,428	19,503

CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio.

All results are probabilistic.

Issues for Consideration

- Patients on inotersen were reported to have a reduced platelet count in the NEURO-TTR study,[4,5] and thrombocytopenia has been noted as a potential risk of treatment.[1] Frequent testing is required to effectively monitor platelet count. The cost of performing blood draws for monitoring would be assumed by the manufacturer as part of the Akcea Connect patient support program.[6] Additionally, platelets need to be measured eight weeks after discontinuation.[1] This may result in additional implementation costs. This was not included in the manufacturer's economic model but would be expected to only marginally increase the ICUR for inotersen.
- To receive inotersen in Canada, the manufacturer requires all patients to enroll in the Akcea Connect patient support program.[2,6] This program offers support to patients, their families, and their health care team, including training on injection administration and education on the required lab testing and monitoring. This program will also provide field nurses to perform blood draws and collect samples for patients according to their health care providers' orders.[2] As a result, the manufacturer's economic model only captured the laboratory fees associated with conducting platelet count, estimated glomerular filtration rate (eGFR), urine protein to creatinine ration (UPCR), and liver monitoring tests.[6]

- The role of liver transplant is unclear. According to the clinical experts consulted by CADTH, it is plausible that patients with hATTR polyneuropathy who receive a liver transplant may continue to use inotersen. The potential cost-effectiveness of inotersen in this clinical population remains unclear, given the existing trials have not studied this patient population.
- Tafamidis may be available through the Health Canada Special Access Programme for patients with transthyretin amyloid cardiomyopathy, although the extent to which it is available and whether it will remain available through the Programme is uncertain. Inotersen was not compared with tafamidis in the manufacturer's economic model.
- The treatment paradigm in patients with hATTR polyneuropathy is quickly shifting. In particular, a new treatment, patisiran, is currently under review by Health Canada. Inotersen was not compared with patisiran in the manufacturer's economic model.

Patient Input

Input for this submission was provided by Hereditary Amyloidosis Canada (HAC). HAC reported on the results of a survey completed by 13 patients, 10 caregivers, and two others (e.g., physicians) along with the results of phone interviews of seven people (six patients and one caregiver) who had experience with inotersen. HAC reported that most respondents had limited ability to perform daily tasks and self-care and some reported that their symptoms limited their ability to work, including some who reported having to leave their job. Some also reported that patients became fully dependent on family members and outside support for their care and survival. The ability to perform daily tasks and self-care is an important part of health-related quality of life and was captured in the model through the utilities.

Patients reported being affected by neuropathy symptoms, gastrointestinal symptoms, sexual dysfunction, and cardiac symptoms. Among survey respondents, 88% reported that nerve damage was severe or incapacitating and 60% reported severe or incapacitating leg swelling, fatigue, shortness of breath, and dizziness. Gastrointestinal symptoms, sexual dysfunction, and cardiac symptoms were not explicitly captured in the model, although it is expected that these effects would be captured in the quality-of-life measure.

More than half of the survey respondents said they (or the patient) had received or were currently receiving treatment specifically for hATTR amyloidosis. One patient had received a liver transplant and others mentioned supportive care (e.g.., for water retention or diarrhea). Many patients mentioned diflunisal but only two felt it was effective in slowing their disease progression. Among those who had been treated with inotersen, the two patients who had been on treatment for more than four years noted an improvement in their quality of life, stating their neuropathy had remained stable or had improved. One patient mentioned the inconvenience of weekly injections and lab visits.

Conclusions

A number of key limitations identified in the manufacturer's model had a large impact on the interpretation of the cost-effectiveness of inotersen. CADTH was unable to address several key limitations, including uncertainties associated with the model structure and the validity in mapping Norfolk TQoL score to Coutinho stage.

Based on the reanalyses that were possible, CADTH's findings were aligned with the manufacturer's: inotersen is not a cost-effective option at a cost-effectiveness threshold of $50,000 per QALY. In adults with hATTR stage I or II polyneuropathy, the CADTH reanalysis estimated the ICUR for inotersen to be $1,322,377 per additional QALY compared with BSC. A price reduction of at least 88% would be required for the ICUR for inotersen to fall below the $50,000 per QALY threshold compared with BSC.

Alternative treatments may become available to patients with this condition (e.g., patisiran); however, the cost-effectiveness of inotersen compared with patisiran is unknown.

Appendix 1: Cost Comparison

The comparators presented in Table 5 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 5: 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 ($)	Recommended Dose	Average Annual Drug Cost ($)
Inotersen (Tegsedi)	189 mg/mL	Pre-filled syringe	8,076.9231[a]	284 mg SC once weekly	420,000

CDR = CADTH Common Drug Review; NOC = Notice of Compliance; SC = subcutaneous.

Note: All prices do not include dispensing fees.[18] First year is assumed to be 52 weeks long.

At the time of the CDR review, no other drug therapies for hereditary transthyretin-mediated amyloidosis with polyneuropathy had been approved for use in Canada. However, it is known that other therapies are currently undergoing a Health Canada review, meaning new comparators may come to market. Specifically, patisiran is currently undergoing a CDR pre-NOC review with the following requested reimbursement criteria: treatment of hereditary transthyretin-mediated amyloidosis with polyneuropathy in adults.

[a] Manufacturer-submitted price.[6]

Table 6: CADTH Common Drug Review Cost-Comparison Table for Products Available Through the Special Access Programme for Adults With Hereditary Transthyretin-Mediated Amyloidosis With Polyneuropathy

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

[a] Dose provided from the European public assessment report for tafamidis.[19]

[b] Annual drug costs for tafamidis were approximated to be $177,216 for the purpose of this review, based on publicly available UK costs. Specifically, to approximate the annual drug cost of tafamidis, the annual cost of inotersen in Canada was adjusted by the relative ratio of the cost of inotersen (£308,100 annually[20]) and the cost of tafamidis (£130,001 annually[21]).

Table 7: 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 ($)	Recommended Dose	Average Annual Drug Cost ($)
Diflunisal	250 mg	Tablet	0.2412[a]	250 mg twice daily[b]	176.08

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

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

Appendix 2: Summary of Key Outcomes

Table 8: When Considering Only Costs, Outcomes, and Quality of Life, How Attractive Is Inotersen Relative to Best Supportive Care?

	Attractive	Slightly Attractive	Equally Attractive	Slightly Unattractive	Unattractive	NA
Costs (total)					✓	
Drug treatment costs alone					✓	
Clinical outcomes		✓				
Quality of life		✓				
Incremental CE ratio (CADTH reanalysis)	$1,322,377 per QALY					

CE = cost-effectiveness; NA = not applicable; QALY = quality-adjusted life-year.

Appendix 3: Additional Information

Table 9: 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”			
Was the submission well organized and was information easy to locate?		✓	
Comments Reviewer to provide comments if checking “poor”			

Table 10: Authors Information

Authors of the Pharmacoeconomic Evaluation Submitted to CDR

☐ 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	X		
Authors had independent control over the methods and right to publish analysis		X	

CDR = CADTH Common Drug Review.

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

Inotersen currently has a positive recommendation for reimbursement listing from France's Haute Authorité de Santé (HAS), which recommended that inotersen be used as a second-line treatment in patients who cannot tolerate patisiran, and that the price of inotersen should be lower than its competitors.[24] No pharmacoeconomic component was included in the HAS review.[25] Inotersen is currently undergoing review by the Scottish Medicines Consortium (expected publication date August 2019).[25,26] The National Institute for Health and Care Excellence in the UK has reviewed inotersen (Table 11).

Table 11: Other Health Technology Assessment Findings

	NICE (2018)[27,28]
Treatment	Inotersen 284 mg SC weekly for hATTR[27]
Price	£5,925 per syringe[28]
Similarities with CDR submission[a]	Similar model conceptualization: • Model structure: Markov cohort state transition model, three living health states based on Coutinho staging[29] • Time: Four-week cycles, 1.5% discount rate, 41-year time horizon[29] • Structural assumptions: Health states defined by TQoL based on Norfolk Quality of Life-Diabetic Neuropathy cut-off scores from Faria et al. (2012)[7]; no improvement at stage III[29] Compared inotersen with BSC[29] Patients discontinue treatment at stage III (i.e., inotersen not given during stage III)[29] Two sets of transition probabilities sourced from NEURO-TTR (35 weeks and 35 to 66 weeks)[29] Time to treatment discontinuation based on NEURO-TTR and NEURO-TTR extension; exponential discontinuation curve chosen to model discontinuation[29] Inotersen administration costs assumed to be £0[29]
Differences with CDR submission[a]	Stage-specific mortality hazard ratios (from Delphi panel) applied to general-population mortality[29] Stewart et al. utilities were not converted to reflect UK value set[29] Two caregivers impacted in all health states[29] Treatment-emergent adverse events excluded[29] Health care resource use based on Swedish clinical expert opinion[27]
Manufacturer's results	Revised base case after clarification, ICUR for inotersen versus BSC: £369,470[b] per QALY[29]
Issues noted by the review group	**Issues Addressed** *By Manufacturer* • Revised utilities to reflect utilities that might be obtained if raw data were available. This involved matching EQ-5D profiles in which the Brazilian tariff was closest to the mean values then applying UK tariffs to the respective EQ-5D profile[30] • Partially implemented cost and disutilities of adverse events[30] • Use of log-logistic distribution to model treatment discontinuation to allow for decreasing rate of discontinuation over time[29] • Lower mortality hazard ratios were applied[30] *By Evidence Review Group* • Used alternative mapping of PND to Coutinho stages to estimate mortality hazard ratios[30] **Issues That Could Not Be Addressed** • Concerns about mapping Norfolk TQoL scores to Coutinho stage • Long-term benefits uncertain[28]
Results of reanalyses by the review group (if any)	The company's updated base case gave an ICUR of £150,636 per QALY gained for inotersen compared with BSC, which includes a confidential price discount[28] The ERG's preferred base-case analysis produced an ICUR of £281,571 per QALY gained (factoring in the confidential price discount)[30]
Recommendation	Inotersen is recommended for treating stage I and stage II polyneuropathy in adults with hATTR[31]

BSC = best supportive care; CDR = CADTH Common Drug Review; EQ-5D = EuroQol 5-Dimensions questionnaire; ERG = evidence review group; hATTR = hereditary transthyretin-mediated amyloidosis; ICUR = incremental cost-utility ratio; NICE = National Institute for Health and Care Excellence; PND = polyneuropathy disability; QALY = quality adjusted life-year; SC = subcutaneous; THAOS = transthyretin amyloidosis outcomes survey; TQoL = total quality of life.

[a] Similarities and differences based on the model submitted by the manufacturer at the clarification stage of the NICE review process.[29]

[b] Exchange rate at time of review was a C$1.7602 = £1.000.[32]

Appendix 5: Reviewer Worksheets

Manufacturer's Model Structure

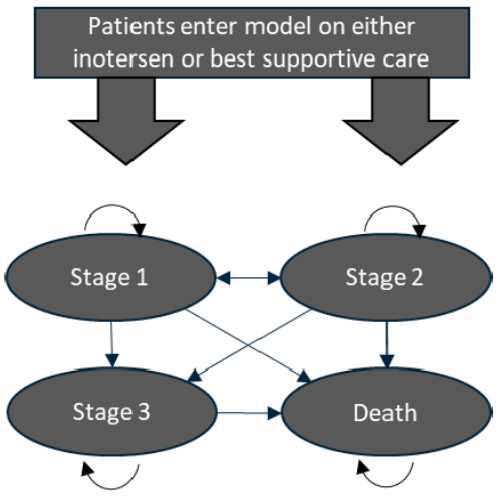
A Markov model was submitted by the manufacturer to assess the cost-effectiveness of inotersen relative to best supportive care (BSC) in the treatment of hereditary transthyretin-mediated amyloidosis (hATTR). Three living health states characterizing hATTR disease progression were developed based on Coutinho's classification which reflects disease progression based on patient mobility:[6]

- Stage I: Patients do not require any assistance with ambulation
- Stage II: Patients require assistance with ambulation (excluding wheelchair)
- Stage III: Patients need a wheelchair or are bedridden

Within stages I and II, patients could be "on treatment," "discontinued (inotersen)," or receiving BSC. Stage III patients may only be "discontinued (inotersen)" or "BSC," since the manufacturer assumed stage III patients do not receive inotersen. Transition probabilities associated with BSC are applied to patients in the BSC arm and to patients who discontinue inotersen.

Patients enter the model distributed across the stage I and II health states based on the initial patient distribution observed in the NEURO-TTR trial (65.7% and 34.3%, respectively).[33] Since inotersen is not indicated for stage III patients, no patients start in Coutinho stage III. Patients enter the model at an initial age of 59 years and 68.6% are male.[33] In each four-week cycle, patients may remain in the same health state, transition to a more severe health state, or die. Patients in stage II receiving inotersen may also improve their health state during the efficacy and extrapolation periods. BSC patients can improve from stage II to I during the efficacy period only.

Figure 1: Model Structure



Source: Manufacturer's pharmacoeconomic submission.[6]

Table 12: Data Sources

Data Input	Description of Data Source	Comment[a]
Baseline characteristics	Baseline characteristics defined in the manufacturer's model were informed by the NEURO-TTR trial.[33]	Appropriate.
Efficacy	*Efficacy period (week 0 to 66):* Transition probabilities were calculated from the NEURO-TTR trial.[33] Patients were assigned into three possible Coutinho health stages based on TQoL cut-off scores for each stage, sourced from Faria et al. (2012).[7] Norfolk QoL-DN scores, a NEURO-TTR trial end point, was the TQoL outcome used: • stage I: 2.6 • stage II: 54 • stage III: 91	According to the CADTH clinical review, the Norfolk QoL-DN score discriminates between patients with and without hATTR and between patients with different stages of hATTR. However, concerns exist with the uncertainty in the cut-off selected. See main report.
	Two sets of transition probabilities were estimated using data from week 0 to week 35 and data from week 35 to week 66. Patients with no TQoL data reported at week 35 or 66 were excluded.	At both the week 35 and week 66 time points, more inotersen patients were excluded from the analysis than placebo patients, suggesting that excluded data were not missing at random.[33] If the patients who were excluded in the inotersen group also had a lower efficacy response, this would favour inotersen. Patients in both the efficacy and extrapolation periods may transition across two health states in a four-week cycle (i.e., patients may transition from stage I to III). Clinical experts consulted by CADTH for this review noted that this would be faster than expected disease progression (see main report).
	Extrapolation period (beyond week 66): Transition probabilities were based on those observed during weeks 36 to 66 of NEURO-TTR.[33] BSC patients could not improve in the extrapolation period.	Uncertain. According to clinical experts consulted by CADTH for this review, there was uncertainty regarding the long-term effects of inotersen treatment.
	Discontinuation: Manufacturer assumed that patients discontinue inotersen upon entering stage III.	Inappropriate. See main report.
	Patients may also discontinue treatment in stages I and II. This was estimated by taking patient-level discontinuation data from the NEURO-TTR and NEURO-TTR extension studies and fitting six parametric distributions.[33] The exponential distribution that used data from NEURO-TTR and the NEURO-TTR extension study was used in the base case.	Goodness-of-fit statistics for the modelled curves using Kaplan–Meier data from NEURO-TTR and NEURO-TTR extension studies showed the lowest BIC for the exponential curve. AIC was not lowest for the exponential curve, indicating that, by this criterion, the Gompertz curve provided a better fit. Visually, both curves appear to fit the Kaplan–Meier discontinuation curve well. As these statistics are unable to assess the appropriateness of the statistical distribution for the extrapolation period, an additional sensitivity analysis was conducted.

Data Input	Description of Data Source	Comment[a]
Natural history	Coutinho disease stages were used to reflect disease progression. TQoL cut-off scores from Faria et al. (2012) were used to map Norfolk QoL-DN scores to Coutinho stage.[7]	Inappropriate. The Faria et al. (2012) report raised several concerns with the approach taken that were not addressed by the manufacturer. These include: • The applicability of Coutinho disease stages developed in a V30M population to a non-V30M or mixed population.[7] It is uncertain if TQoL changes at the same rate for V30M and non-V30M patients. • Issues regarding the assumption that Coutinho disease stages can be defined by TQoL scores. TQoL cut-off scores used to define stages were based on data observed in the THAOS registry. The rules selected were considered arbitrary and lacking in supporting evidence.[7]
Utilities	Utilities were sourced from Stewart et al. (2017), which studied a mixed (V30M and non-V30M) hATTR patient population in Brazil.[10] To derive Canadian utilities, the manufacturer chose one or two EQ-5D profiles with a Brazilian tariff–based value that was closest to the mean disease stage value and then applied Canadian tariffs[16] to the selected EQ-5D profile. Utilities for patients on inotersen increased by 0.0002 for each cycle they remained in the same health state, while the utility of BSC patients decreased by 0.0038 for each cycle they remained in the same state,[6] according to the observed difference in utility from baseline to the end of the NEURO-TTR trial.[33] Caregiver disutility was applied to all patients. Disutilities were sourced from Gani et al. (2008), which estimated caregiver disutility for multiple sclerosis.[34] The disutility for AEs occurring in the model was based on manufacturer assumptions and from the literature and other reports.[35,36,37]	Inappropriate approach. See main report. Inappropriate. Based on the CADTH *Guidelines for the Economic Evaluation of Health Technologies: Canada* (4th edition), treatment-specific utility values are not considered to be an appropriate approach.[9] See main report. Inappropriate. See main report. Some AEs were not assigned disutility values. This would favour inotersen, given the AE profile observed in the trial. This approach is inappropriate but unlikely to impact the model. AE disutilities are not included in the probabilistic analysis.
AEs (indicate which specific AEs were considered in the model)	Only serious treatment-emergent AEs that were considered to be related to the study drug were considered in the model. Rates were based on the NEURO-TTR study.[33]	The manufacturer noted that the serious AEs observed with inotersen, such as thrombocytopenia and renal impairment, are mitigated by monitoring. Clinical experts consulted for this review also note that patient and physician education and close monitoring should help mitigate the increased risks of thrombocytopenia and glomerulonephritis associated with inotersen treatment that were observed in the trial. Experts also noted that patients may be reluctant to adhere to biweekly platelet monitoring.

Data Input	Description of Data Source	Comment[a]
Mortality	Calculated as a hazard ratio[38] comparing hATTR patient mortality with that of the Canadian general population. An additional multiplier[39] was applied by disease stage, with an increased mortality risk associated with more advanced stages.	Inappropriate. According to clinical experts consulted by CADTH for this review, patients are unlikely to experience an increased mortality risk according to their polyneuropathy stage. The manufacturer provided an option of estimating mortality based on survival curves for V30M and non-V30M patients. (Source: Sattianayagam et al., 2011.[11]) In appraising this approach, reviewers noted several limitations: • The non-V30M population in this study all had the T60A variant. The representativeness of this variant in comparison with all non-V30M patients is unknown. • The manufacturer chose to use the Weibull curve for both the V30M and non-V30M populations. However, the goodness-of-fit statistics demonstrate that for the non-V30M population, other curves had lower AIC and BIC, indicating that another statistical distribution may have provided a better fit in this population.
Resource Use and Costs		
Drug	Price of inotersen from the manufacturer.[6] Price of vitamin A supplementation was not included in the base case.	Appropriate.
Administration	Assumed to be zero.	Appropriate. As per inotersen's product monograph, it is intended to be administered by the patient.[1] Additionally, the manufacturer of inotersen will introduce a patient support program (Akcea Connect) to assist patients in learning how to self-administer the drug. (Source: CADTH Common Drug Review for inotersen.[2])
Monitoring	No monitoring assumed at start of treatment. Monitoring while on treatment with inotersen included: platelet count every two weeks, eGFR and UPCR tests every 3 months, and annual hepatic enzyme testing. Costs of laboratory tests were sourced from the Ontario Schedule of Benefits for Laboratory Services (2017),[40] while the cost of phlebotomist's time was considered in scenario analysis only.	Inotersen's product monograph recommends measuring platelet count, eGFR, UPCR, and plasma vitamin A prior to initiation. Although not considered, not incorporating monitoring at treatment initiation is unlikely to impact the model. Inappropriate. Private phlebotomy labs still receive funding from public payers; therefore, this cost could be considered in the base case, although this is unlikely to influence the model results.

Data Input	Description of Data Source	Comment[a]
AEs	Costs were obtained from the CIHI Information Patient Cost Estimator.[41]	This is an appropriate source for AE costs. However, several concerns were noted: • Reviewers were unable to validate all costs using the CIHI Patient Cost Estimator. • Some AEs were not assigned costs. • Some codes used may be inappropriate for the AE. • Costs estimates from CIHI were taken from all age groups, not just adult patients. Despite the concerns noted in the approach used to estimate AE costs, this is unlikely to impact the model results.
Health state	Costs included in the health-state estimates were separated into costs relating to polyneuropathy, gastrointestinal disorders, cardiac arrhythmias, bladder or ocular dysfunction, primary care, aids, home care, and hospitalization. For each category, it may include labour costs,[42,43] monitoring costs,[40,42] medication costs,[18] home care,[44] hospitalization costs,[41] or other resources.[45]	Appropriate.
	The frequency of occurrence of each of these costs was estimated from interviews with Canadian clinicians experienced in treating hATTR patients.	Uncertain. According to clinical experts consulted by CADTH for this review, the frequency of some specialist visits may differ from what is observed in their practice, although this is unlikely to impact the model.
	A multiplier of 43% was added to reduce recurrent health care–related costs in stage I and II patients receiving inotersen, based on a manufacturer assumption that those receiving inotersen would experience lower health care–related costs than those on BSC, even when patients are within the same health state. (Source: NICE appraisal of patisiran.[39])	Clinical experts consulted by CADTH noted that differences in costs would be treatment-related (i.e., monitoring, AE management). This should be considered as part of treatment-related costs (i.e., drugs, AEs, administration, monitoring), which have been correctly calculated for inotersen but not for BSC. Although this approach is inappropriate and imprecise, the magnitude of bias that it would introduce is uncertain. See details in the main report.

A1C = glycated hemoglobin; AE = adverse event; AIC = Akaike information criteria; BIC = Bayesian information criteria; BSC = best supportive care; CIHI = Canadian Institute for Health Information; eGFR = estimated glomerular filtration rate; EQ-5D = EuroQol 5-Dimensions questionnaire; ERG = Evidence Review Group; hATTR = hereditary transthyretin-mediated amyloidosis; NICE = National Institute for Health and Care Excellence; Norfolk QoL-DN = Norfolk Quality of Life-Diabetic Neuropathy; THAOS = Transthyretin Amyloidosis Outcomes Survey; TQoL = total quality of life; UPCR = urine protein to creatinine ratio.

Table 13: Manufacturer's Key Assumptions

Assumption	Comment
Coutinho disease stages are an appropriate classification to describe disease progression in a mixed (V30M and non-V30M) hATTR population.	Coutinho stages were developed in a V30M population. Their applicability in a non-V30M population is unknown.
TQoL scores can be used to define Coutinho disease stages.[7]	Cut-off scores used to define disease stages were sourced from a report evaluating the cost-effectiveness of tafamidis by Faria et al.[7] This report specifies that cut-offs were based on TQoL scores and disability levels from the Transthyretin-Associated Amyloidosis Outcome Survey (THAOS) Registry.[7] This study used the mPDS, which assesses walking ability, to convert to Coutinho stages without providing justification for the mapping of mPDS to Coutinho disease stage.[7] Additionally, there are several concerns regarding using TQoL scores to stratify patients, as scores are subjective and some improvement in scores might be possible, especially for patients near the cut-offs. Further, there is significant heterogeneity in TQoL for each stage.
TQoL rates of change are the same for V30M and non-V30M patients.	Uncertain.
Patients discontinue inotersen upon entering stage III.	Inappropriate. According to clinical experts consulted by CADTH for this review, physicians are unlikely to discontinue treatment with inotersen for patients based on their need to use a wheelchair, as patients may have residual motor or sensory function in upper limbs that may benefit from treatment with inotersen.
Patients cannot improve upon entering stage III.	This is appropriate under the assumption that patients discontinue treatment in stage III. It is uncertain whether patients will improve if continuing to receive treatment in stage III. Clinical experts expressed uncertainty regarding the treatment effect of inotersen in stage III patients.
BSC patients cannot improve in the extrapolation period.	According to clinical experts consulted by CADTH for this review, they would not expect patients receiving BSC alone to demonstrate improvement in their Coutinho stage. However, using the manufacturer's approach to modelling disease progression, some BSC patients showed improvements in their Coutinho stages in both the efficacy and extrapolation periods, highlighting the limited validity of this approach. However, it is considered invalid that BSC patients may not improve in the extrapolation period while patients receiving inotersen may.
Treatment efficacy observed in weeks 35 to 66 in the NEURO-TTR trial was assumed to continue for the patient's lifetime.	Clinical experts expressed uncertainty regarding the long-term effects of inotersen.
hATTR patients do not receive a liver transplant.	The role of liver transplant and whether patients would continue to be administered inotersen is unclear. According to clinical experts consulted by CADTH, less than 10% of patients currently will receive a liver transplant.
Polyneuropathy disease accounts for all patient progression and mortality.	Inappropriate. According to clinical experts consulted by CADTH, increased mortality is attributable to cardiomyopathy, which was not explicitly considered in the manufacturer's model.
90% treatment compliance.	Uncertain. Prescriptions may continue to be filled even if patients are not taking their medication all of the time and the effect on costs to the health care system is unclear. Assuming compliance is lowered for inotersen, this would lower the expected treatment costs, favouring inotersen.

BSC = best supportive care; hATTR = hereditary transthyretin-mediated amyloidosis; mPDS = modified polyneuropathy disability score; TQoL = total quality of life.

Manufacturer's Results

In the manufacturer's base case, treatment with inotersen compared with BSC was associated with an additional cost of $1,165,042 and a quality-adjusted life-year (QALY) gain of 1.28, resulting in an incremental cost-utility ratio (ICUR) of $523,448 per QALY (Table 2).

CADTH Common Drug Review Reanalyses

CADTH conducted eight scenario analyses using alternative assumptions relating to the CADTH base case:

1. Incorporating the dosing reported in NEURO-TTR (i.e., inotersen costs reduced by 10% to reflect missed doses in NEURO-TTR)
2. Using manufacturer's utility values (i.e., the values from Stewart et al.[10] converted to Canadian values using methods described in the main report)
3. Assuming all patients discontinue inotersen upon entering stage III
4. Using a log-logistic curve to estimate treatment discontinuation rates
5. Assuming mortality rates based on the population of patients with the V30M mutation
6. Assuming mortality rates based on the non-V30M population
7. Using the treatment efficacy reported during week 0 to week 35 in order to extrapolate efficacy beyond the NEURO-TTR trial period
8. Assuming that patients receiving inotersen will have the same transition probabilities in the extrapolation period as patients receiving BSC.

Table 14 presents the results of these scenario analyses.

Table 14: CADTH Common Drug Review Scenario Analyses

Scenario		Treatments	QALYs	Cost ($)	Cost per QALY ($)
	CADTH base-case reanalysis	BSC	2.19	255,497	1,322,377
		Inotersen	2.99	1,318,508	
1	**CADTH base case, 90% compliance**	BSC	2.18	268,649	1,141,468
		Inotersen	3.00	1,205,500	
2	**CADTH base case, manufacturer's utility values**	BSC	2.32	258,487	1,298,478
		Inotersen	3.14	1,325,994	
3	**CADTH base case, discontinuation inotersen in stage III**	BSC	2.21	268,466	1,226,521
		Inotersen	3.02	1,266,200	
4	**CADTH base case, log-logistic discontinuation curve**	BSC	2.19	1,521,979	1,350,089
		Inotersen	3.12	268,734	
5	**CADTH base case, patients with V30M**	BSC	2.46	316,484	1,172,674
		Inotersen	3.44	1,465,200	
6	**CADTH base case, patients with non-V30M**	BSC	1.88	216,345	1,489,322
		Inotersen	2.52	1,164,336	
7	**CADTH base case, extrapolation of treatment efficacy based on efficacy reported at week 0 to 35**	BSC	1.95	291,812	1,557,272
		Inotersen	2.63	1,353761	

Scenario		Treatments	QALYs	Cost ($)	Cost per QALY ($)
8	**CADTH base case, with same benefits assumed after 66 weeks**	BSC	2.18	268,723	3,171,765
		Inotersen	2.53	1,372,944	

BSC = best supportive care; QALY = quality-adjusted life-year.

Scenario analyses demonstrate that the model remained robust across most scenario analyses. The model was most sensitive to the assumption on long-term treatment effects. In the final scenario, where the treatment effects of inotersen were applied only during the observed period and no additional improvements were assumed between inotersen and BSC after the trial period (week 66), the ICUR for inotersen compared with BSC was found to increase to more than $3.1 million per QALY gained (Table 14).

References

1. Tegsedi (inotersen): 284 mg inotersen / 1.5 mL persyringe [189 mg inotersen / mL (as inotersen sodium)] injection[product monograph]. Boston (MA): Akcea Therapeutics, Inc.; 2018 Oct 2: http://www.akceatx.ca/wp-content/uploads/2018/10/FINAL-Pristine-PM_02OCT2018.pdf. Accessed 2019 Jun 1.
2. CDR submission: Tegsedi (inotersen), 284 mg inotersen/1.5 mL per syringe [189 mg inotersen/mL (as inotersen sodium)], solution for injection [**CONFIDENTIAL** manufacturer's submission]. Ottawa (ON): Akcea Therapeutics, Inc.; 2019 Feb 22.
3. Adams D. Recent advances in the treatment of familial amyloid polyneuropathy. *Ther Adv Neurol Disord.* 2013;6(2):129-139.
4. Benson MD, Dasgupta NR, Monia BP. Inotersen (transthyretin-specific antisense oligonucleotide) for treatment of transthyretin amyloidosis. *Neurodegener Dis Manag.* 2019;9(1):25-30.
5. Clinical study report: ISIS 420915-CS2. A phase 2/3 randomized, double-blind, placebo-controlled study to assess the efficacy and safety of ISIS 420915 in patients with familial amyloid polyneuropathy (NEURO-TTR study) [CONFIDENTIAL internal manufacturer's report]. Carlsbad (CA): Ionis Pharmaceuticals, Inc; 2017 Oct 2.
6. Pharmacoeconomic evaluation. In: CDR submission: Tegsedi (inotersen), 284 mg inotersen / 1.5 mL persyringe [189 mg inotersen / mL (as inotersen sodium)] injection [**CONFIDENTIAL** manufacturer's submission]. Ottawa (ON): Akcea Therapeutics Inc.; 2019.
7. Faria R, Walker S, Palmer S, Corbett M, Stirk L, McDaid C. Tafamidis for transthyretin familial polyneuropathy (TTR-FAP) evidence review group assessment of manufacturer submission. University of York: York (UK); 2012: https://www.york.ac.uk/media/crd/Tafamidis%20ERG%20Report_CRDCHE%20September%204%202013.pdf. Accessed 2019 Jun 1.
8. Adams D, Suhr OB, Hund E, et al. First European consensus for diagnosis, management, and treatment of transthyretin familial amyloid polyneuropathy. *Curr Opin Neurol.* 2016;29 Suppl 1:S14-26.
9. 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 May 5.
10. Stewart M, Mundayat R, Alvir J, et al. Clinical characteristics and health state utilities in patients with transthyretin familial amyloid polyneuropathy in Brazil. Poster presented at the International Society for Pharmacoeconomics and Outcomes Research - 22nd International Meeting, May 20-24, 2017, Boston, MA, United States. 2017.
11. Sattianayagam PT, Hahn AF, Whelan CJ, et al. Cardiac phenotype and clinical outcome of familial amyloid polyneuropathy associated with transthyretin alanine 60 variant. *Eur Heart J.* 2012;33(9):1120-1127.
12. Suhr O, Danielsson A, Holmgren G, Steen L. Malnutrition and gastrointestinal dysfunction as prognostic factors for survival in familial amyloidotic polyneuropathy. *J Intern Med.* 1994;235(5):479-485.
13. Vinik EJ, Vinik AI, Paulson JF, et al. Norfolk QOL-DN: validation of a patient reported outcome measure in transthyretin familial amyloid polyneuropathy. *J Peripher Nerv Syst.* 2014;19(2):104-114.
14. Ando Y, Coelho T, Berk JL, et al. Guideline of transthyretin-related hereditary amyloidosis for clinicians. *Orphanet J Rare Dis.* 2013;8:31.
15. 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 Jun 1.
16. Bansback N, Tsuchiya A, Brazier J, Anis A. Canadian valuation of EQ-5D health states: preliminary value set and considerations for future valuation studies. *PLoS One.* 2012;7(2):e31115.
17. Brooks R. EuroQol: the current state of play. *Health Policy.* 1996;37(1):53-72.
18. Ontario Ministry of Health and Long-Term Care. Ontario drug benefit formulary/comparative drug index. 2018; https://www.formulary.health.gov.on.ca/formulary/. Accessed 2019 Feb 15.
19. EPAR summary for the public: vyndaqel (tafamidis). London (GB): European Medicines Agency; 2016: https://www.ema.europa.eu/en/documents/overview/vyndaqel-epar-summary-public_en.pdf. Accessed 2019 Jun 24.
20. National Institute for Health and Care Excellence. Evaluation consultation document: Inotersen for treating hereditary transthyretinrelated amyloidosis. 2018; https://www.nice.org.uk/guidance/hst9/documents/evaluation-consultation-document. Accessed 2019 June 1.
21. National Institute for Health Research. Tafamidis for transthyretin amyloid cardiomyopathy. *(NIHR Innovation Observatory ID: 5124)*. Newcastle upon Tyne (UK): Newcastle University; 2018: http://www.io.nihr.ac.uk/wp-content/uploads/2018/06/5124-Tafamidis-for-TTR-CM-V1.0-JUN2018-NON-CONF.pdf. Accessed 2019 May 15.
22. Government of British Columbia. BC PharmaCare formulary search. 2018; https://pharmacareformularysearch.gov.bc.ca. Accessed 2019 Jun 1.
23. Boston University. NCT00294671: The effect of diflunisal on familial amyloidosis. *ClinicalTrials.gov*. Bethesda (MD): U.S. National Library of Medicine; 2006: https://clinicaltrials.gov/ct2/show/NCT00294671. Accessed 2019 Mar 1.
24. Haute Authorité de Santé (HAS). Commission de la transparence avis 17 avril 2019: inotersen. Saint-Denis (France): Haute Authorité de Santé (HAS); 2019.

25. Haute Authorité de Santé (HAS). Décision n° 2019.0004/DC/SEESP du 9 janvier 2019 du collège de la Haute Autorité de santé constatant l'impact significatif du produit Tegsedi 284 mg (inotersen) sur les dépenses de l'assurance maladie. Saint-Denis (France): Haute Authorité de Santé (HAS); 2019: https://www.has-sante.fr/portail/upload/docs/application/pdf/2019-01/dc_2019.0004_eco_effi_tegsedi_cd_2019_01_09_vd.pdf. Accessed 2019 Apr 11.

26. Inotersen (tegsedi). *(SMC No. 2188)*. Glasgow (GB): Scottish Medicines Consortium: https://www.scottishmedicines.org.uk/medicines-advice/inotersen-tegsedi-full-smc2188/. Accessed 2019 Apr 11.

27. National Institute for Health and Care Excellence. Highly specialised technology evaluation: inotersen for treating hereditary transthyretin-related amyloidosis ID1242. Evaluation report. 2018; https://www.nice.org.uk/guidance/hst9/evidence/evaluation-consultation-committee-papers-pdf-6782713166. Accessed 2019 Jun 1.

28. National Institute for Health and Care Excellence. Final evaluation document: inotersen for treating hereditary transthyretinrelated amyloidosis. 2019; https://www.nice.org.uk/guidance/hst9/documents/final-evaluation-determination-document. Accessed 2019 Jun 1.

29. National Institute for Health and Care Excellence. Lead team presentation. Inotersen for treating hereditary transthyretin amyloidosis, 1st evaluation committee meeting. 2018; https://www.nice.org.uk/guidance/hst9/documents/1. Accessed 2019 Jun 1.

30. National Institute for Health and Care Excellence. Inotersen for treating hereditary transthyretin-related amyloidosis. Chair's presentation, 2nd evaluation committee meeting. 2019; https://www.nice.org.uk/guidance/hst9/documents/1-2. Accessed 2019 Jun 1.

31. National Institute for Health and Care Excellence. Inotersen for treating hereditary transthyretin amyloidosis. *(Highly specialised technologies guidance HST9)* 2019; https://www.nice.org.uk/guidance/hst9/chapter/1-Recommendations. Accessed 2019 May 27.

32. Bank of Canada. Monthly exchange rates. 2019; https://www.bankofcanada.ca/rates/exchange/monthly-exchange-rates/. Accessed 2019 June 1.

33. Ionis Pharmaceuticals. Clinical study report: ISIS 420915-CS2. A phase 2/3 randomized, double-blind, placebo-controlled study to assess the efficacy and safety of ISIS 420915 in patients with familial amyloid polyneuropathy (NEURO-TTR study). [**CONFIDENTIAL** manufacturer's submission]. Carlsbad (CA): Isis Pharmaceuticals, Inc.; 2017 Oct 2.

34. Gani R, Giovannoni G, Bates D, Kemball B, Hughes S, Kerrigan J. Cost-effectiveness analyses of natalizumab (Tysabri®) compared with other disease-modifying therapies for people with highly active relapsing-remitting multiple sclerosis in the UK. *Pharmacoeconomics.* 2008;26(7):617-627.

35. Tolley K, Goad C, Yi Y, Maroudas P, Haiderali A, Thompson G. Utility elicitation study in the UK general public for late-stage chronic lymphocytic leukaemia. *Eur J Health Econ.* 2013;14(5):749-759.

36. National Institute for Health and Care Excellence. Apixaban for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism. *(Technology appraisal guidance TA341)* 2015; https://www.nice.org.uk/guidance/ta341/resources/apixaban-for-the-treatment-and-secondary-prevention-of-deep-vein-thrombosis-andor-pulmonary-embolism-pdf-82602602803141. Accessed 2019 Apr 26.

37. Akcea Therapeutics, Inc. response to April 11th 2019 CDR request for additional information regarding the Tegsedi CDR review [**Confidential** additional manufacturer's information]. Ottawa (ON): Akcea Therapeutics, Inc.; 2019 Apr 16.

38. Coelho T, Ericzon B-G, Falk R, Grogan D. Physician's guide to transthyretin amyloidosis. 2008.

39. National Institute for Health and Care Excellence. Highly specialised technology evaluation: patisiran for treating hereditary transthyretin amyloidosis ID1279. Evaluation report. 2018.

40. Ontario Ministry of Health and 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 Jun 1.

41. Canadian Institute for Health Information. Patient cost estimator. 2019; https://www.cihi.ca/en/patient-cost-estimator. Accessed 2019 Apr 1.

42. Ontario Ministry of Health and Long-Term Care. Schedule of benefits for physician services under the Health Insurance Act: effective December 21, 2015. 2015; http://www.health.gov.on.ca/english/providers/program/ohip/sob/physserv/physserv_mn.html. Accessed 2019 Jun 1.

43. Ontario Ministry of Health Long-Term Care. Schedule of benefits for optometry services. 2009; http://www.health.gov.on.ca/en/pro/programs/ohip/sob/optometry/sob_optometrist_services_20090401.pdf. Accessed 2019 Jun 1.

44. Wodchis W, Bushmeneva K, Nikitovic M, McKillop I. Guidelines on person-level costing using administrative databases in Ontario. *(Working paper series volume 1)*. Toronto (ON): Health System Performance Research Network; 2013: https://tspace.library.utoronto.ca/bitstream/1807/87373/1/Wodchis%20et%20al_2013_Guidelines%20on%20Person-Level%20Costing.pdf. Accessed 2019 Jun 1.

45. Ontario Case Costing Initiative (OCCI). 2017; https://www.ontario.ca/data/ontario-case-costing-initiative-occi. Accessed 2019 Jun 1.