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CADTH COMMON DRUG REVIEW

Pharmacoeconomic Review Report

TAFAMIDIS (Vyndaqel)

(Pfizer Canada ULC)

Indication: For the treatment of adult patients with cardiomyopathy due to transthyretin-mediated amyloidosis, wild-type or hereditary, to reduce cardiovascular mortality and cardiovascular-related hospitalization.

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

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Table of Contents

Tables

Figure

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Abbreviations

AE	adverse event
AIC	Akaike's information criterion
ATTR-CM	transthyretin-mediated amyloidosis cardiomyopathy
BIC	Bayesian information criterion
BSC	best supportive care
CUA	cost-utility analysis
EQ-5D	EuroQol 5-Dimensions
ICUR	incremental cost-utility ratio
ITT	intention to treat
NYHA	New York Heart Association
QALY	quality-adjusted life-year
WTP	willingness to pay

Table 1: Summary of the Sponsor's Economic Submission

Drug product	Tafamidis meglumine (Vyndaqel)
Study question	What is the incremental cost-effectiveness of tafamidis meglumine compared with BSC in the treatment of adult patients with cardiomyopathy due to transthyretin-mediated amyloidosis (wild-type or hereditary)?
Type of economic evaluation	Cost-utility analysis
Target population	Adult patients with cardiomyopathy due to transthyretin-mediated amyloidosis, wild-type or hereditary
Treatment	Tafamidis meglumine 80 mg daily
Outcome	QALYs
Comparator	BSC, consisting of supportive care medication
Perspective	Canadian public health care payer
Time horizon	Lifetime (30 years)
Results for base case	ICUR = $247,069 per QALY gained compared with BSC
Key limitations	• Disease progression, in terms of mortality and cardiovascular-related hospitalization, occurred as a function of a patient's baseline NYHA class rather than their current NYHA class. This approach has limited clinical validity and likely resulted in overestimation of the survival benefits associated with tafamidis meglumine. • Treatment discontinuation and efficacy were modelled independently. The approach to model each was incongruent, as ongoing reductions in treatment acquisition costs were extrapolated beyond the 30-month trial period, whereas long-term efficacy estimates were based on an intention-to-treat analysis at months 18 to 30 of the ATTR-ACT trial. • The ATTR-ACT trial measured treatment response every six months, whereas the economic model was based on a monthly cycle. During the first 30 months of the model, patients could transition only at the end of each six-month period. This is likely unrealistic in practice and adds uncertainty to the efficacy estimates. • Treatment-specific health state utility values were used. • Resource-use estimates may not reflect expected treatment practices, as patients in NYHA class IV in Canada would be expected to see nephrologists and have more frequent primary care visits. • Treatment costs were reduced by assuming lower rates of adherence, which is inappropriate, as patients are still likely to fill prescriptions. • Uncertainty remains as to the long-term clinical efficacy of tafamidis meglumine and the initiation of tafamidis meglumine at an advanced disease stage (i.e., NYHA class IV), due to a paucity of clinical data.
CDR estimate(s)	The CADTH reanalysis: selected different distributions for the survival curves; assumed an identical duration for each hospitalization event; capped treatment discontinuation at 30 months; removed treatment-specific health state utilities; revised resource-use estimates in accordance with current clinical practices; and assumed 100% adherence. • Based on these revisions, CADTH found that the ICUR of tafamidis meglumine compared with BSC was $443,694 per QALY gained. • A price reduction of at least 92% would be required for tafamidis meglumine to be considered cost-effective at a willingness-to-pay threshold of $50,000 per QALY. CADTH was unable to fully address several structural limitations. Uncertainty further remains regarding the clinical efficacy of tafamidis meglumine beyond 30 months, given the uncertainty in the long-term evidence. The potential cost-effectiveness of tafamidis meglumine in patients in NYHA class IV at baseline could not be assessed.

BSC = best supportive care; CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; NYHA = New York Heart Association; QALY = quality-adjusted life-year.

Drug	tafamidis meglumine (Vyndaqel)
Indication	For the treatment of adult patients with cardiomyopathy due to transthyretin-mediated amyloidosis, wild-type or hereditary, to reduce cardiovascular mortality and cardiovascular-related hospitalization.
Reimbursement request	Treatment of transthyretin amyloid cardiomyopathy in adult patients.
Dosage form(s) and route of administration) and strength(s)	20 mg capsule
NOC date	January 20, 2020
Sponsor	Pfizer Canada ULC

Executive Summary

Background

Tafamidis meglumine (Vyndaqel) is indicated for the treatment of adult patients with cardiomyopathy due to transthyretin-mediated amyloidosis, wild-type or hereditary, to reduce cardiovascular mortality and cardiovascular-related hospitalizations. Tafamidis meglumine is available as a 20 mg capsule with a recommended dose of 80 mg daily. At the sponsor's submitted price of $133.57 per capsule, the daily and annual drug cost is $534.28 and $195,012, respectively, per patient.[1]

The sponsor submitted a cost-utility analysis (CUA) comparing tafamidis meglumine with best supportive care (BSC) in the treatment of adults with both wild-type or hereditary transthyretin-mediated amyloidosis cardiomyopathy (ATTR-CM).[1] BSC was informed by the placebo arm of the ATTR-ACT trial, which permitted patients to continue taking medications considered to be standard of care, such as diuretics.[2] The analysis was conducted from the perspective of the Canadian publicly funded health care payer over a lifetime horizon (30 years) using one-month cycles.[1] Future costs and benefits were discounted at a rate of 1.5% per year.[1] A multi-state cohort Markov model was developed with three main health states: "alive without transplant," "alive with transplant," and "death."[1] Within the "alive without transplant" health states, patients were further subdivided into the four New York Heart Association (NYHA) classes to reflect cardiac disease progression. Every six months during the first 30 months of treatment, and monthly thereafter, patients could transition to any NYHA class.[1] Clinical efficacy was based on the ATTR-ACT trial.[2] At any point, patients in the "alive without transplant" health states could receive a heart transplant (i.e., enter the "alive with transplant" health state).[1] This health state consisted of two tunnel health states: a "one-month post-transplant" state, and a "greater than or equal to two months post-transplant" state.[1] The probability of transitioning to the "alive with transplant" health states were dependent on both current NYHA class and treatment arm, informed by data from the ATTR-ACT trial.[1] Mortality for patients in the "alive without transplant" health states were estimated separately by baseline NYHA class (i.e., NYHA class I/II and NYHA class III subgroups) and by treatment arm, based on the extrapolated all-cause overall survival observed in the ATTR-ACT trial.[2] Gompertz curves were applied for the BSC arm in patients with baseline NYHA class I/II or NYHA class III, while gamma curves were applied for the tafamidis meglumine arm in baseline NYHA class I/II and NYHA class III patients.[2] Mortality for patients in the "alive with transplant" health state was informed by survival data calculated from the International Society for Heart and Lung Transplantation registry.[3]

Treatment-specific utilities by NYHA class were derived from the EuroQol 5-Dimensions (EQ-5D) data collected in the ATTR-ACT trial.[2] Health state utilities for patients in the "alive with transplant" health states were sourced from a UK cost-effectiveness study.[4] Costs in the model included treatment acquisition costs, which were adjusted by the extrapolated treatment discontinuation and compliance data from the ATTR-ACT trial.[1,2] No treatment costs were assumed to be associated with BSC.[1] Background disease management in the form of visits to a cardiologist, other physician specialists (including neurology and gastroenterologist visits), primary care and emergency room visits, were included based on NYHA class. Costs associated with cardiovascular-related hospitalizations were included, using the treatment and subgroup-specific probabilities for hospitalizations and durations of stay reported in the ATTR-ACT trial.[2] No utility decrements for hospitalizations were included in the CUA.[1]

The sponsor reported that the incremental cost-utility ratio (ICUR) for tafamidis meglumine was $247,069 per quality-adjusted life-year (QALY) compared with BSC.

Summary of Identified Limitations and Key Results

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

Disease progression was a function of the patient's baseline NYHA class rather than their current NYHA class. For instance, the probability of experiencing a cardiovascular-related hospitalization, as well as the duration of a hospitalization event, was dependent on a patient's baseline NYHA class and treatment. According to the clinical experts, these parameters are not expected to differ by treatment and, rather than their NYHA class at baseline, a patient's current NYHA class is more predictive of these clinical events. In addition, mortality for those in the "alive without transplant" health states was estimated from separate survival curves derived based on baseline NYHA class (i.e., NYHA class I/II and NYHA class III) and treatment (i.e., tafamidis meglumine and BSC). According to clinical experts consulted for this review, this resulted in overly optimistic survival estimates for patients receiving tafamidis meglumine and overly pessimistic survival estimates for patients receiving BSC.

Two issues arise with the independent modelling of treatment discontinuation and efficacy. In the longer-term extrapolation (i.e., beyond 30 months), this resulted in ongoing decreases in treatment costs with no reduction in tafamidis meglumine's treatment effects. Furthermore, given the probabilistic analysis, these inputs were randomly sampled with no correlation assumed. This meant that it was possible during iterations of the analysis that higher rates of discontinuation were sampled alongside improved efficacy estimates. This has limited clinical plausibility. The model also inappropriately incorporated the trial efficacy data: despite using one-month cycle lengths, the model cycled the "alive without transplant" group every six months during the trial observation period (i.e., 30 months). Also, treatment-specific health state utilities were used for the "alive with transplant" group. This is considered inappropriate.[5]

According to experts consulted by CADTH for this review, resource utilization estimates may not reflect expected treatment practices, as patients may be expected to see nephrologists and have more frequent primary care visits in later disease stages. In addition, treatment costs for tafamidis meglumine were reduced by 2.2% by assuming that patients were 97.8% adherent to treatment. This is inappropriate, as patients are expected to still fill their full prescriptions despite missing doses.

There is uncertainty as to the long-term effects of treatment and the effects in advanced disease stages (i.e., NYHA class IV). These uncertainties limit the interpretation of the results from the economic model.

CADTH attempted to address the previously mentioned limitations by: using a Weibull survival function to estimate mortality for patients with baseline NYHA class I/II; using a Gompertz survival function to estimate morality for patients with baseline NYHA class III; capping treatment discontinuation at 30 months; removing treatment-specific utilities; adding the costs of nephrology visits and increasing the frequency of primary care visits in patients in NYHA class IV; and assuming that patients are fully adherent to treatment.

Based on the CADTH reanalyses, tafamidis meglumine was $895,494 more expensive and yielded an additional 2.02 QALYs, resulting in an ICUR of $443,694 per QALY gained compared with BSC.

Conclusions

CADTH identified a number of key limitations with the sponsor's submission. Based on reanalyses, CADTH's findings were aligned with the sponsor's, as tafamidis meglumine was found to not be a cost-effective option at a willingness-to-pay (WTP) threshold of $50,000 per QALY. Compared with no treatment, tafamidis meglumine resulted in an ICUR of $443,694 per QALY gained. In order for tafamidis meglumine to be considered cost-effective at a WTP threshold of $50,000 per QALY, a price reduction of at least 92% would be required.

Subgroup analysis by baseline NYHA class indicates that tafamidis meglumine may be associated with a lower ICUR in less severe disease stages. In patients initiating treatment at NYHA class I/II, the ICUR was $411,053 per QALY gained compared with BSC whereas, in patients initiating treatment at NYHA class III, the ICUR was $699,242 per QALY compared with BSC.

CADTH was unable to fully address several structural limitations of the submitted economic model (i.e., mortality rates and the probability of cardiovascular-related hospitalization were dependent on the patient's baseline NYHA class; independent modelling of discontinuation and efficacy data; and inappropriate implementation of efficacy transitions during the first 30 months of the model).

Uncertainty exists for the clinical efficacy of tafamidis meglumine beyond 30 months, given the uncertainty of long-term clinical evidence. The potential cost-effectiveness of tafamidis meglumine in patients with baseline NYHA class IV is unknown and was not addressed in either the sponsor's or CADTH's analyses.

Information on the Pharmacoeconomic Submission

Summary of the Sponsor's Pharmacoeconomic Submission

The sponsor submitted a CUA comparing tafamidis meglumine 80 mg with BSC in the treatment of patients with transthyretin-mediated amyloidosis cardiomyopathy (ATTR-CM).[1] BSC was informed by the placebo arm of the ATTR-ACT trial, which permitted medications considered to be standard of care, such as diuretics.[2] Specifically, in the ATTR-ACT trial, regarding standard of care medications, patients were stabilized for at least four weeks prior to the trial baseline. All patients were permitted to use supplements and medications throughout the course of the study, apart from the drugs that were prohibited in the study protocol (see CADTH clinical report).[2] The sponsor considered a lifetime time horizon (30 years) and the analysis was conducted from the perspective of a Canadian publicly funded health care payer, discounting costs and outcomes (QALYs) at a rate of 1.5% per annum.[1] The model reflected a population with the same baseline characteristics as those reported in the ATTR-ACT trial (89% male; average age of 75 years; 67% of patients in NYHA class I/II; and 33% of patients in NYHA class III).[2]

A multi-state, cohort Markov model using monthly cycles was submitted by the sponsor that consisted of three broad health states: "alive without transplant," "alive with transplant," and "death" (Figure 1).[1] The "alive with transplant" health state was further subdivided by the four NYHA classes to model disease progression.[1] The NYHA classes describe heart failure symptoms and limitations experienced during physical activity.[6] The functional classification for each NYHA class can be described as:

- NYHA class I: No symptoms and no limitations in ordinary physical activity.[7]
- NYHA class II: Mild symptoms and slight limitation during ordinary activity.[7]
- NYHA class III: Marked limitation in activity due to symptoms, even during less-than-ordinary activities. Comfortable only at rest.[7]
- NYHA class IV: Severe limitations. Experience symptoms even while at rest.[7]

Patients entered the model in one of two subgroups based on baseline NYHA status:

- NYHA class I/II, in which 12% of patients started treatment in NYHA class I and 88% started treatment in NYHA class II
- NYHA class III.[1]

The model runs the two subgroups separately and the results are weighted by the baseline NYHA class distributions (i.e., 67% in NYHA class I/II and 33% in NYHA class III) to produce the full population's cost-effectiveness estimates.[1] Within the "alive without transplant" health states, patients may improve, remain the same, or worsen.[1] For the first 30 months of the model time horizon (reflecting the length of the ATTR-ACT trial), patient transitions between NYHA classes were based on six-month observations from the intention-to-treat population (ITT).[1] Beyond 30 months, transitions were extrapolated from the transitions observed between months 18 and 30 of the ATTR-ACT trial.[1]

Only patients within the "alive without transplant" health states were assumed to be treated with tafamidis meglumine. From those health states, patients could transition to the "alive with transplant" health state.[1] NYHA class-specific and treatment-specific probabilities for

heart transplantation (which informed the transition to the "alive with transplant" health state), were informed by data from the ATTR-ACT trial.[2] In effect, transplants occurred in patients on tafamidis meglumine in NYHA class II to IV, whereas transplants occurred in patients receiving BSC in NYHA class II or III. Tunnel states were used to represent the disease progression post-transplantation, as this permitted applying different mortality rates for the first month and subsequent months of the procedure. Specifically, patients first entered the "one-month post-transplant" health state and, if they survived the first month post-transplant, they entered a "greater than or equal to two months post-transplant" health state.[1] Once in the "alive with transplant" health state, patients could not transition back to the "alive without transplant" health states, and their health status and disease progression were assumed to be modelled entirely in the "greater than or equal to two months post-transplant" health state (see Figure 1).[1] Additionally, patients who received transplants were assumed to no longer receive treatment with tafamidis meglumine.[1]

Patients could transition to death from any health state. Treatment-dependent mortality for patients in the "alive without transplant" health states were estimated separately for baseline NYHA class I/II and class III subgroups from the extrapolated all-cause overall survival curves from the ATTR-ACT trial.[2] Gompertz survival functions were selected for the BSC arm and gamma survival function were selected for the tafamidis meglumine arm.[1] Mortality for patients in the "alive with transplant" health states were informed by a study by Lund et al., which reported survival data from the International Society for Heart and Lung Transplantation registry.[3] From this study, the sponsor calculated that patients would have a 7.7% and a 0.6% probability of dying in the first month and in subsequent months, respectively, following a heart transplant.[1]

EuroQol 5-Dimensions 3-Levels (EQ-5D-3L) data, collected from the ATTR-ACT trial and applying a Canadian valuation set,[1] were used to estimate NYHA health state utility values by treatment arm.[2] Health state utilities for patients in the "alive with transplant" health state were sourced from a cost-effectiveness study that used the EQ-5D-3L to measure utility, based on a UK valuation set.[4] Utility decrements for adverse events (AEs) and hospitalizations were not incorporated in the model.[1]

The model included treatment acquisition costs for tafamidis meglumine, which were adjusted based on parametric extrapolation of the treatment discontinuation data from the ATTR-ACT trial based on an exponential distribution.[1] Patients remained on treatment irrespective of their NYHA classes unless they discontinued.[1] Standard of care in Canada for ATTR-CM patients is understood to include treatment with diuretics and antiarrhythmic medications; these costs were not included in the model and, therefore, no treatment costs were associated with receiving BSC. Other costs included AE management costs, cardiovascular-related hospitalization costs, transplant costs, and end-of-life care costs; costs were based on Canadian sources.[8] All "alive without transplant" patients had a per-cycle probability of having a cardiovascular-related hospitalization, by baseline NYHA class and by treatment arm, based on the rates observed in the ATTR-ACT trial.[2] Durations of hospitalizations were also sourced from ATTR-ACT and were similarly stratified by baseline NYHA class and treatment arm.[2] The frequency of background disease management visits, by current NYHA class, was estimated from a survey of two Canadian ATTR-CM specialists[1] and included visits to cardiologists, other specialists, primary care, and the emergency room. Upon transitioning to the death state, all patients were assumed to incur a one-time end-of-life cost, which was sourced from an Ontario study examining the cost-effectiveness of heart failure clinics.[9]

Sponsor's Base Case

The sponsor assumed that 67% and 33% of patients have a baseline NYHA class of I/II and class III, respectively. Separate models were conducted for these subgroups (i.e., NYHA class I/II and NYHA class III) with results then being weighted to reflect the proportion of patients initiating treatment in each subgroup. The sponsor found that, compared with BSC, tafamidis meglumine was $790,379 more expensive and yielded an additional 3.20 QALYs, resulting in an ICUR of $247,069 per QALY gained (Table 2).[1] At a WTP threshold of $50,000 per QALY, there is a 0% probability of tafamidis meglumine 80 mg being optimal.[1]

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

	Tafamidis meglumine (a)	BSC (b)	Difference (a minus b)
QALYs	**5.21**	**2.01**	**3.20**
LYs	7.07	2.85	4.23
Costs	**$**	**$**	**$**
Drug acquisition	741,485	0	741,485
Adverse events	149	179	−30
CV-related hospitalizations	29,129	20,004	9,125
Background management	15,325	6,797	8,528
End of life	1,308	1,400	−92
Total costs	**833,282**	**42,903**	**790,379**
$ per QALY			$247,069

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

Source: Sponsor's pharmacoeconomic submission.[1]

Summary of Sponsor's Sensitivity Analyses

Uncertainty was examined through scenario analyses, including:

- applying different discount rates
- setting different time horizons
- selecting alternative distributions for the parametric survival curves for tafamidis meglumine and BSC
- selecting a Gompertz distribution to estimate treatment discontinuation
- capping treatment discontinuation at month 30 (i.e., no additional patients discontinue after the trial period)
- using all-cause hospitalization costs instead of cardiovascular-related hospitalization costs
- conducting a multi-cohort sensitivity analysis, with an increasing proportion of patients starting with a baseline NYHA class I/II to reflect increasing awareness of ATTR-CM following the introduction of tafamidis meglumine

The results of the sponsor's scenario analyses demonstrated that the model was most sensitive to the time horizon selected, the extrapolated survival curves, and capping treatment discontinuation to the end of the trial period. The results of these select scenario analyses are presented in Appendix 5 (Table 12).

Limitations of Sponsor's Submission

- **Disease progression was a function of baseline NYHA values rather than current NYHA values:** For those in the "alive without transplant" health states, the sponsor's model structure was based on baseline NYHA classes to predict disease progression. Several clinical parameters within the model (i.e., probability of hospitalization, duration of hospitalization, mortality) depended on a patient's baseline NYHA class rather than their current NYHA class. According to clinical experts consulted by CADTH for this review, a patient's existing NYHA class is a more reasonable predictor for these clinical events than a patient's NYHA class at baseline.

  The probability of cardiovascular-related hospitalization and the duration of hospitalization were specific to a patient's baseline NYHA class and not to their current NYHA class. Thus, all patients within the same treatment arm that began in the same baseline NYHA subgroup would have the same probability of being hospitalized or the same duration of stay, regardless of their current NYHA class. This is not consistent with what would be expected clinically. For patients currently in the same NYHA class, they would not be expected to have differences in hospitalization due to their baseline NYHA values. Additionally, according to clinical experts consulted by CADTH for this review, a patient's duration of hospitalization would not differ by treatment arm or initial NYHA class, but would be expected to differ by their current NYHA class. The face validity of the sponsor's estimates is further limited, as values suggested a shorter hospitalization duration for those with baseline NYHA class III than those with baseline NYHA class I/II. A more appropriate approach would have been to model the probability of cardiovascular-related hospitalization and its associated duration of stay dependent on patients' current NYHA class rather than their NYHA class at baseline. Reviewers were unable to incorporate probabilities of cardiovascular-related hospitalizations or durations of hospitalizations based on current NYHA class due to a lack of data to support these estimates. CADTH removed treatment and subgroup-specific duration of hospitalization by taking a weighted average of these estimates in reanalyses.

  In addition, the sponsor used baseline subgroup data from the ATTR-ACT trial (i.e., baseline NYHA class I/II and NYHA class III) to estimate mortality based on extrapolated survival curves.[2] Within the trial period, the impact of a patient's current NYHA class on mortality would be reflected, as the proportion of patients who have progressed to higher NYHA classes would be implicitly captured in the within-trial mortality trends. However, in the extrapolation period, these dependencies would not be captured in the analysis, as the proportion of patients who have progressed to higher NYHA classes would not be explicitly reflected in the extrapolation, reducing the validity of the extrapolations produced. The selection of the statistical distribution to model overall survival is further questionable. Patients in the NYHA class I/II and NYHA class III subgroups who initiated tafamidis meglumine were both modelled with a gamma survival function; those in the NYHA class I/II and class III subgroups who received BSC were modelled according to a Gompertz survival function. According to the sponsor, the gamma distribution was selected for patients on tafamidis meglumine, given it had the best statistical fit among the overall survival curves that were deemed to be clinically plausible.[1] While the gamma distribution was associated with the lowest Akaike's information criterion (AIC) and Bayesian information criterion (BIC) for the NYHA class I/II tafamidis meglumine subgroup, the Gompertz distribution, in fact, had a lower AIC and BIC in the NYHA class III tafamidis meglumine subgroup. Furthermore, according to clinical experts consulted by CADTH for this review, there is limited face validity with selecting the gamma distribution. A small proportion of tafamidis meglumine patients

remained alive at 100 years of age in the baseline NYHA class I/II subgroup (2.5%) according to this distribution; ATTR-CM patients receiving tafamidis meglumine would not be expected to survive beyond 25 years if they were assumed to initiate treatment at 75 years of age.[1] By selecting the gamma distribution, this would predict more optimistic survival outcomes than would be expected, according to the clinical experts consulted on this review. According to the sponsor, the Gompertz distribution was selected for a similar rationale for patients on BSC group: it was a clinically plausible curve with the best statistical fit. While the Gompertz distribution was associated with the lowest AIC and BIC for the NYHA class I/II BSC subgroup, the Weibull curve, in fact, was associated with a lower AIC and BIC in the NYHA class III subgroup. Using the Gompertz survival function for BSC patients resulted in a 0% probability of survival after six years for NYHA class I/II and NYHA class III patients.[1] Although clinical experts consulted for this review reported heterogeneity in the disease progression, untreated patients in NYHA class I/II at baseline would be expected to have a mean survival of five to 10 years. By selecting the Gompertz distribution for both subgroups, this may result in the economic model predicting worse survival outcomes for BSC than would be expected, according to clinical experts consulted on this review. Together, the distributions selected to model overall survival likely resulted in optimistic survival estimates for tafamidis meglumine and pessimistic survival estimates for BSC. A more appropriate approach to estimate mortality would have been to calculate a mortality risk for patients based on current NYHA class rather than by estimating mortality using survival curves that reflect baseline NYHA classes. Furthermore, the sponsor's approach to select identical statistical forms to model overall survival by treatment is poorly justified. CADTH consulted clinical experts who proposed alternative statistical distributions that they felt would be more clinically plausible and which still had appropriate statistical fit.

- **Discontinuation and efficacy were modelled independently:** The model structure did not explicitly consider the effect of treatment discontinuation and compliance on efficacy. In the ATTR-ACT trial, 21.6% of tafamidis meglumine 80 mg patients discontinued treatment due to reasons other than death by the end of the trial period.[1] According to the CADTH clinical report, the main reasons for discontinuing, aside from death, were due to withdrawal of consent and AEs.

  The sponsor reports that survival, hospitalization, utility, and disease progression inputs to the economic model were derived from the ITT analysis of the ATTR-ACT trial, which considered the outcomes of patients allocated to tafamidis meglumine regardless of discontinuation.[1] However, the sponsor's approach to model discontinuation and efficacy parameters independently of each other is concerning. When conducting probabilistic analyses, this would not preserve the likely correlation between these two sets of parameters in the economic model. Instead, in probabilistic analysis, discontinuation and efficacy would be sampled independently, implying that these two parameters are uncorrelated. This meant that in any one draw of the probabilistic analysis, more patients may have discontinued tafamidis meglumine, but efficacy estimates may be separately drawn to be higher. The contrary could also occur, whereby, in any one draw, fewer patients may have discontinued tafamidis meglumine but lower efficacy estimates may be drawn randomly. Both of these scenarios would have limited face validity. During the review, CADTH requested that the sponsor provide a revised model that would separately model those who remain on treatment from those who have discontinued to allow users to separately track the patients who had discontinued from treatment.[10] The sponsor acknowledged that efficacy and discontinuation inputs are presently being sampled independently and proposed an approach to avoid this issue by setting discontinuation

parameters to be deterministic.[10] This is not appropriate, as it does not allow the potential uncertainty within this model parameter to be adequately characterized.

Additionally, the sponsor adjusted tafamidis meglumine treatment costs by the proportion of patients remaining on tafamidis meglumine therapy. This was estimated using the extrapolated discontinuation data from the ATTR-ACT trial and further assumed that patients would discontinue treatment beyond the observed trial period.[2] However, long-term efficacy estimates were based on the clinical data observed during months 18 to 30 of the ATTR-ACT trial. This approach is inconsistent, as discontinuation was extrapolated to continue to occur beyond 30 months; thereby, drug costs continued to be reduced, while efficacy estimates reflected efficacy under the discontinuation rates that were observed from months 18 to 30 of the ATTR-ACT trial. By cycle 92 (i.e., 7.6 years) for tafamidis meglumine patients with baseline NYHA class I/II, the efficacy data informing the economic model remained based on that observed from months 18 to 30 of the trial (at which time, approximately 20% of tafamidis meglumine patients had discontinued for reasons other than death); however, the model assumed that treatment discontinuation by cycle 92 would be 50%. Hence, treatment acquisition costs would only apply to 50% of the "alive without transplant" patients. This means that treatment costs have been underestimated by more than 50%. CADTH partially addressed this issue. Given that efficacy estimates for the ITT population were extrapolated from months 18 to 30, discontinuation was similarly modelled to occur up to month 30 with no further treatment discontinuation assumed after month 30.

- **Inappropriate approach to modelling transitions during the trial period:** During the first 30 months of the model, transitions for patients in the "alive without transplant" group were based on data from the ATTR-ACT trial in which[1] trial observations were made at six-month assessment time points. The submitted model employed one-month cycle lengths.[1] In order to model patients for the first 30 months, the sponsor used patient's distributions observed at every six-month interval to determine the number of patients moving between NYHA classes and assumed that transitions occurred only at the observed trial periods. For example, for the first six months of the model, the distribution of patients by NYHA class remained identical to their baseline distributions. After the first six months, the distribution changed based on the reported trial results.[1] Patient distribution by NYHA class was then assumed to remain constant for months six to 11 until the trial's next observed assessment time point (i.e., 12 months). This approach lacks precision by assuming patients only transition at six-month time points. It is unlikely in real practice that transitions between NYHA class would only occur at six-month intervals.
- **Use of treatment-specific health state utilities:** To describe disease progression, the "alive without transplant" state was further subdivided by NYHA classification. NYHA classes describe heart failure symptoms and limitations experienced during physical activity. A post-hoc analysis of EQ-5D data collected in the ATTR-ACT trial by treatment arm was used to estimate health state utility values using a Canadian value set.[1] The use of treatment-specific utility values is contradictory to CADTH's *Guidelines for the Economic Evaluation of Health Technologies: Canada,* which recommends that utilities should reflect the health states in the model.[5] The use of treatment-specific utility values means that patients receiving tafamidis meglumine who occupy the same NYHA class as those receiving BSC will have a different quality of life. According to clinical experts consulted by CADTH, quality of life would be expected to differ by NYHA class; however, patients on tafamidis meglumine compared with patients on BSC who are in the same NYHA class would not be expected to have differences in quality of life. The application of treatment-specific utility values is expected to favour tafamidis meglumine, given tafamidis

meglumine was associated with higher utility values for the NYHA class II, class III, and class IV health states and the large majority of time is spent in these health states. The CADTH reanalyses removed treatment-specific utility values by calculating weighted-average utility values by NYHA class, and these were subsequently applied to the model regardless of treatment assignment.

- **Resource-use estimates may not reflect expected treatment practices:** When calculating background management costs in the model, only health care resource use in the form of physician visits and hospitalizations was included. According to clinical experts consulted by CADTH for this review, the background management estimates submitted by the sponsor differ from current Canadian clinical practice. Clinical experts noted that the frequency of patient visits to neurologists and gastroenterologists is not expected to vary by NYHA class, which was assumed in the sponsor's model, whereby more severe patients, by NYHA class, had more frequent visits. Clinical experts also reported that approximately half of NYHA class III and IV patients would likely visit their nephrologists every three months for assistance with managing cardiac symptoms. These physician costs were not considered in the model. Experts also reported that NYHA class IV patients may see nurse practitioners in cardiovascular clinics every month. Revised estimates of the costs of background disease management were calculated based on this feedback and are presented in Appendix 5 (Table 14).
- **Reduction in costs due to lower adherence:** To estimate per-cycle tafamidis meglumine treatment costs, the sponsor calculated the cost per day based on their submitted price for tafamidis meglumine and the relative dose intensity. In the ATTR-ACT trial, patients in the tafamidis meglumine 80 mg arm were reported to receive 97.8% of doses (i.e., patients took 97.8% of doses versus the number of doses expected).[2] In the sponsor's model, the cost of tafamidis meglumine was therefore decreased by 2.2%. However, prescriptions for tafamidis meglumine may continue to be filled even if patients are not fully adherent to treatment. Assuming that adherence is lowered for tafamidis meglumine would reduce expected treatment costs and therefore favour tafamidis meglumine.
- **Uncertain long-term clinical efficacy and in advanced disease stages:** At the time of this review, there were limited clinical data on the use of tafamidis meglumine in patients with NYHA class IV. The ATTR-ACT trial excluded patients with NYHA class IV at screening or baseline visits.[2] As such, the efficacy and cost-effectiveness of initiating tafamidis meglumine in NYHA class IV is unknown. Additionally, to extrapolate efficacy estimates, the treatment effects observed during months 18 to 30 were used to estimate tafamidis meglumine treatment efficacy for the entire model time horizon. According to the CADTH clinical review, there is an ongoing open-label extension study for tafamidis meglumine; however, there is uncertainty in the clinical data available for this study. At the time of this review, as there is uncertainty in the long-term tafamidis meglumine efficacy data beyond 30 months, the long-term treatment effects of tafamidis meglumine assumed in the model remain highly uncertain.
- **Use of an arbitrary coefficient of variation:** For many cost parameters, including the cost per hospitalized day, AE costs, background management costs, end-of-life costs, and health state costs for tunnel states in the "alive with transplant" health state, the standard error was fixed to be 10% of the mean estimate.[1] In addition, standard errors for mortality rates and health state utility values for the "alive with transplant" health states were also fixed at 10% of the mean estimates.[1] Using fixed standard errors means that the probabilistic results may not fully reflect the true uncertainty around model parameters. The arbitrary assumption in defining probability distributions is inappropriate, as

parameters with low sensitivity but higher uncertainty should impact the model's output more than more sensitive parameters that are estimated more precisely.[5] A more appropriate approach would have been to calculate the standard error surrounding the parameter or to use estimates of variability in the parameter from the original source of the parameter. Reviewers were unable to source standard errors from the literature; therefore, this limitation could not be addressed.

CADTH CDR Reanalyses

CADTH could not fully address limitations associated with model inputs being dependent on baseline NYHA class (i.e., mortality rates, probability of hospitalization, durations of hospital stay); the lack of correlation between discontinuation and efficacy; inappropriate approach to transitions in the first 30 months; uncertainties regarding long-term clinical efficacy and in advanced disease stages; or use of an arbitrary coefficient of variation for some parameters.

CADTH conducted the following reanalyses to address some of the key limitations described previously:

1. a) Removed treatment-specific cardiovascular-related hospitalization duration.
   b) Selected alternative statistical distribution to model overall survival curves based on both statistical fit and clinical expert consultation. Weibull curves were selected for the NYHA class I/II subgroups for both tafamidis meglumine and BSC, while Gompertz curves were selected for the NYHA class III subgroup for both tafamidis meglumine and BSC patients.
2. Capped treatment discontinuation at month 30 (no further discontinuation beyond the trial period).
3. Removed treatment-specific utility values.
4. a) Added costs of nephrologist visits to background disease management costs.
   b) Increased frequency of primary care visits in NYHA class IV.
5. Assumed patients are fully adherent to treatment.

The CADTH reanalyses demonstrate that selecting alternative curves to estimate mortality and capping discontinuation at month 30 had the largest effect on the ICUR, increasing the ICUR to $339,175 and $325,184, respectively (Table 3). The model was robust to changes made to the cost of background disease management and the duration of hospitalization.

Compared with the sponsor's results, the CADTH reanalysis estimated lower expected QALYs for tafamidis meglumine (CADTH base case: 4.39 QALYs; sponsor's base case: 5.21 QALYs), but higher expected QALYs for BSC (CADTH base case: 2.37; sponsor's base case: 2.01) (full results provided in Table 15). The expected costs were higher for both tafamidis meglumine and BSC. In the CADTH reanalysis, the ICUR for tafamidis meglumine was $433,694 per additional QALY gained compared with BSC (Table 3).

Table 3: CDR Reanalysis of Limitations

	Description	Sponsor's base case value	CDR value	Incremental cost ($)	Incremental QALYs	ICUR ($/QALY)
	Sponsor's base case	**Reference**		**790,379**	**3.20**	**247,069**
1a	Duration of cardiovascular-related hospitalization	Specific to treatment arm and baseline NYHA class	Identical (9.1 days)	792,499	3.20	247,732
1b	Survival curves, estimated by treatment arm	Gamma selected for tafamidis meglumine for both subgroups (i.e., baseline NYHA class I/II and III) Gompertz selected for BSC for both subgroups	Weibull curve for tafamidis meglumine and BSC's baseline NYHA class I/II subgroups; Gompertz curve for tafamidis meglumine and BSC's baseline NYHA class III subgroup	718,719	2.12	339,175
2	Treatment discontinuation	Costs of tafamidis meglumine reduced based on extrapolated trial discontinuation data over the entire model time horizon	No reduction in costs due to treatment discontinuation after month 30	1,040,272	3.20	325,184
3	"Alive without transplant" health state utility values	Utility values are from ATTR-ACT trial data and are treatment-specific	Weighted average of treatment-specific utility values calculated and applied to both treatment arms	793,902	3.15	252,207
4a	Background management: Other specialist visits	Costs of nephrologist visits not included	Costs of nephrologist visits included for NYHA class III and class IV, as per clinical expert input	790,832	3.20	247,210
4b	Background management: Primary care visits	Costs of nurse practitioner visits in NYHA class IV not included	Costs of primary care visits increased in NYHA class IV, as per clinical expert input	790,380	3.20	247,069
5	Treatment adherence	97.8%	100%	807,059	3.20	252,283
6	**CADTH base case (1 to 5)**			**895,495**	**2.02**	**443,694**

BSC = best supportive care; CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; NYHA = New York Heart Association; QALY = quality-adjusted life-year.

The following scenario analyses were conducted to explore additional sources of uncertainty:

Scenario analysis A: Assuming the entire population starts treatment in NYHA class I/II or and NYHA class III. Since the sponsor divided the model population into subgroups by baseline NYHA class, reviewers examined the cost-effectiveness of tafamidis meglumine in each subgroup individually.

Scenario analysis B: Removing costs of AE management from the analysis. The AEs included in the model were pre-specified AEs of clinical importance. In ATTR-ACT, these AEs occurred in greater frequency in BSC patients than in tafamidis meglumine patients. The frequency of AEs in both treatment arms was reduced to zero in order to explore the effect of AE costs on model results.

Scenario analysis C: No transplants. Clinical experts consulted by CADTH for this review noted that transplants as a means of treating ATTR-CM are uncommon in Canada. Therefore, in this scenario, the probability of receiving transplants in all NYHA classes and treatment arms was reduced to zero.

Scenario analysis D: No difference in the probability of hospitalization. As mentioned in the key limitations, reviewers were unable to address the issue of the probability of a cardiovascular-related hospitalization being independent of a patient's current NYHA class. Instead, the probability of hospitalization depends on both the treatment arm and the subgroup. To explore the impact of hospitalization on the model results, the probability of a patient experiencing cardiovascular-related hospitalization in the BSC group was made equal to the probability of cardiovascular-related hospitalization in the tafamidis meglumine group.

Scenario analysis E: Using the sponsor's estimate for treatment adherence. Given the uncertainty in how treatment adherence will influence expected tafamidis meglumine costs, CADTH reviewers examined a scenario whereby the treatment adherence observed in the ATTR-ACT trial (97.8%) was used to estimate tafamidis meglumine costs.

The full results of the CADTH scenario analyses are presented in Table 16. The model was fairly stable across most scenarios. The ICUR for tafamidis meglumine in patients at baseline NYHA class I/II was lower than in those at baseline with NYHA class III ($411,053 compared with $699,242 per QALY gained), indicating that tafamidis meglumine would be expected to have a lower ICUR in less severe disease stages.

Price-reduction analyses on the CADTH base case found that, in order for tafamidis meglumine to be considered cost-effective at a WTP threshold of $50,000 per QALY, a 92% price reduction would be required (Table 4).

Table 4: CDR Reanalysis Price-Reduction Scenarios

ICURs of submitted drug versus comparator		
Price	**Base-case analysis submitted by sponsor ($)**	**Reanalysis by CDR ($)**
Submitted	247,069	443,694
70% reduction	84,819	143,058
80% reduction	61,641	100,314
90% reduction	**38,463**	57,452
92% reduction	33,827	**49,011**
95% reduction	26,873	36,309

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

Issues for Consideration

- An alternative tafamidis meglumine formulation, Vyndamax, is available in the US but is not currently available in Canada.
- According to the clinical panel conducted by CADTH for this review, tafamidis meglumine could theoretically be used in combination with medications used to manage polyneuropathy in patients with hereditary transthyretin-mediated amyloidosis, including patisiran and inotersen, given their different mechanism of action. However, no clinical evidence regarding combination therapy is available; therefore, the cost-effectiveness of tafamidis meglumine in combination with these other medications is unknown.

- According to the clinical panel conducted by CADTH for this review, diagnosing ATTR-CM is challenging. If patients are misdiagnosed as having ATTR-CM, this may lead to inappropriate use of tafamidis meglumine. Misdiagnosis was outside the scope of this review but, if considered, would be expected to result in a higher ICUR than that estimated in CADTH reanalyses.

Patient Input

Input for this submission was provided by the Canadian Organization for Rare Disorders with support from the Canadian Amyloidosis Support Network. An online survey (n = 42) and individual patient interviews (n = 4) described the experience of patients and/or their caregivers with wild-type, hereditary, or suspected ATTR-CM. The Canadian Organization for Rare Disorders reported that almost all patients or caregivers reported ATTR-CM to be debilitating, interfering with patient's daily functioning and quality of life. The cardiac-specific symptoms reported by patients included shortness of breath, lower extremity swelling, palpitations, arrhythmia, and chest pain; the severity of these symptoms was heterogeneous, ranging from serious or incapacitating to infrequently experienced. Patients reported that their symptoms influenced their ability to work and their capacity for physical exertion. Given that capacity for physical exertion is captured by NYHA class, the sponsor's submission partially captures the concerns raised by patients.

With respect to current therapies for ATTR-CM, patients noted that, aside from tafamidis meglumine, no specific therapies to treat ATTR-CM were available. Patients reported a broad range of medications to manage symptoms associated with ATTR-CM, including diuretics and medications to manage mineral levels. Patients also received medications to manage blood pressure, regulate heartbeat, and prevent blood clots. One-third of patients were currently using diflunisal, a nonsteroidal anti-inflammatory medication, and another third reported having previously used this drug. Among those with experience with diflunisal, two-thirds of patients reported a moderate or poor treatment effect with diflunisal, while the remainder felt that it worked well. In the sponsor's model, no active treatment comparators were included in the sponsor's economic analysis of tafamidis meglumine; therefore, the cost-effectiveness of tafamidis meglumine compared with diflunisal is unknown.

Almost half (39%) of participants had received tafamidis meglumine. Patients reported benefits in terms of symptom management, including a reduction in nerve pain, an increase in strength and energy, an improvement in appetite, and an improvement in mobility. The EQ-5D-3L measure does collect many of these dimensions of health. Patients also reported a slowing or halting of disease progression, allowing patients to do more in their daily lives. This treatment effect was modelled in the sponsor's CUA, as patients may remain in the same NYHA class, improve their NYHA class, or worsen from their existing NYHA class.

Conclusions

CADTH identified a number of key limitations with the sponsor's submission. Based on reanalyses, CADTH's findings were aligned with the sponsor's, as tafamidis meglumine was found to not be a cost-effective option at a WTP threshold of $50,000 per QALY. Compared with no treatment, tafamidis meglumine resulted in an ICUR of $443,694 per QALY gained. In order for tafamidis meglumine to be considered cost-effective at a WTP threshold of $50,000 per QALY, a price reduction of at least 92% would be required.

Subgroup analysis by baseline NYHA class indicates that tafamidis meglumine may be associated with a lower ICUR in less severe disease stages. In patients initiating treatment at NYHA class I/II, the ICUR was $411,053 per QALY gained compared with BSC whereas, in patients initiating treatment at NYHA class III, the ICUR was $699,242 per QALY compared with BSC.

CADTH was unable to fully address several structural limitations of the submitted economic model (i.e., mortality rates and probability of cardiovascular-related hospitalization were dependent on patient's baseline NYHA class; independent modelling of discontinuation and efficacy data; inappropriate implementation of efficacy transitions during the first 30 months of the model).

Uncertainty exists for the clinical efficacy of tafamidis meglumine beyond 30 months, given the uncertainty in the long-term clinical evidence. The potential cost-effectiveness of tafamidis meglumine in patients with baseline NYHA class IV is unknown and was not addressed in either the sponsor's or CADTH's analyses.

Appendix 1: Cost Comparison

The comparators presented in the following table 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 sponsor 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: CDR Cost Comparison Table for Drug Therapies for Adults With Cardiomyopathy Due to Transthyretin-Mediated Amyloidosis, Wild-Type or Hereditary

Drug/comparator	Strength	Dosage form	Price ($)	Recommended dose	Average daily drug cost ($)	Average annual drug cost ($)
Tafamidis meglumine (Vyndaqel)	20 mg	Capsule	133.5700[a]	80 mg once daily	534.28	195,012

CDR = CADTH Common Drug Review.

[a] Sponsor-submitted price.

Table 6: CDR Cost Comparison Table for Off-Label Drug Therapies for Adults With Cardiomyopathy Due to Transthyretin-Mediated Amyloidosis, Wild-Type or Hereditary

Drug/comparator	Strength	Dosage form	Price ($)	Recommended dose	Average daily drug cost ($)	Average annual drug cost ($)
Diflunisal	250 mg	Tablet	0.2412[a]	250 mg twice daily[b]	0.48	176.08

CDR = CADTH Common Drug Review.

[a] Price from British Columbia PharmaCare Formulary (accessed August 20, 2019).[11]

[b] Recommended daily dose from a clinical trial examining the effect of diflunisal on familial amyloidosis.[12] The appropriateness of this dose was confirmed with the CADTH clinical experts consulted for this review.

Appendix 2: Summary of Key Outcomes

Table 7: When Considering Only Costs, Outcomes, and Quality of Life, How Attractive Is Tafamidis Meglumine Relative to Best Supportive Care?

Tafamidis meglumine versus best supportive care	Attractive	Slightly attractive	Equally attractive	Slightly unattractive	Unattractive	NA
Costs (total)					X	
Drug treatment costs alone					X	
Clinical outcomes		X				
Quality of life		X				
ICUR	Sponsor's ICUR: $247,069 per QALY CADTH's revised ICUR: $443,694 per QALY					

ICUR = incremental cost-utility ratio; NA = not applicable; QALY = quality-adjusted life-year.

Appendix 3: Additional Information

Table 8: Submission Quality

	Yes/ Good	Somewhat/ Average	No/ Poor
Are the methods and analysis clear and transparent?		X	
Comments Reviewer to provide comments if checking “no”	Several of the cost inputs used in the model could not be validated according to the reported sources. It was further unclear whether tafamidis meglumine 80 mg or pooled tafamidis meglumine was used to inform long-term transition probabilities.		
Was the material included (content) sufficient?	X		
Comments Reviewer to provide comments if checking “poor”	None		
Was the submission well organized and was information easy to locate?	X		
Comments Reviewer to provide comments if checking “poor”	None		

Table 9: Authors Information

Authors of the pharmacoeconomic evaluation submitted to CADTH

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

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

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

☒ Other (please specify): Sponsor’s developed the economic analysis

	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

Appendix 4: Summary of Other Health Technology Assessment Reviews of Tafamidis Meglumine

Tafamidis meglumine is currently being reviewed by the National Institute for Health and Care Excellence (NICE) and the Institut national d'excellence en santé et en services sociaux (INESSS).[13,14] Results of these reviews are not yet available. The expected publication date for the NICE review of tafamidis meglumine is June 10, 2020.[13]

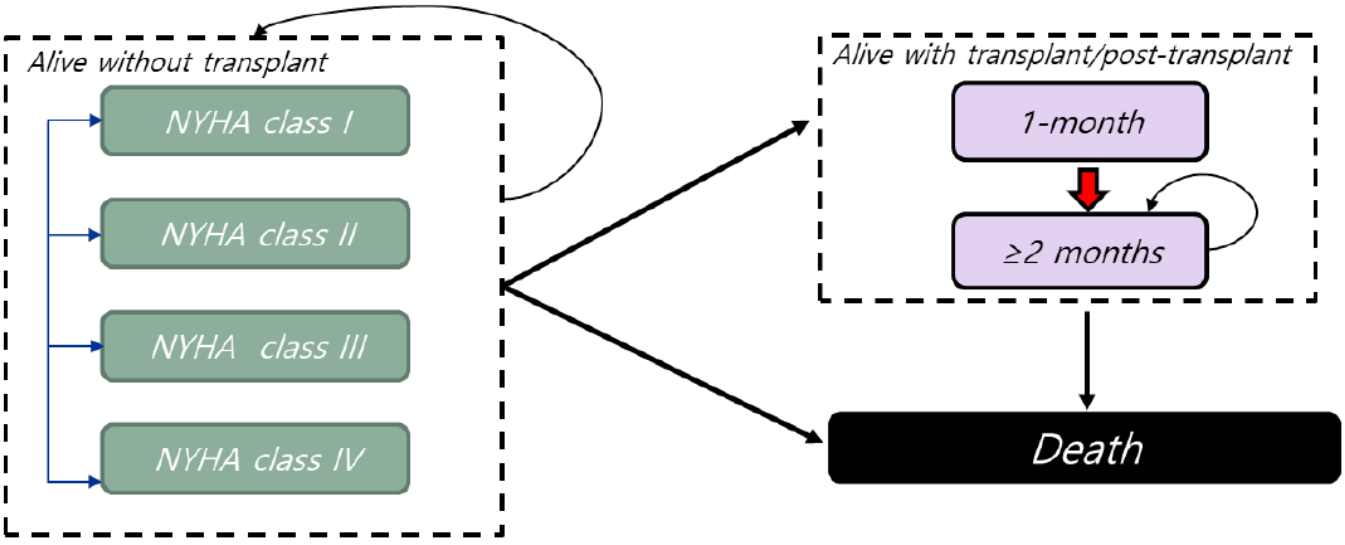
Appendix 5: Reviewer Worksheets

Sponsor's Model Structure

The sponsor submitted a multi-state cohort Markov model to assess the cost-effectiveness of tafamidis meglumine compared with BSC in patients with transthyretin-mediated amyloidosis cardiomyopathy (ATTR-CM). The Markov model divided patients into three broad health states: "alive without transplant," "alive with transplant," and "death" (the absorbing health state).[1] The "alive without transplant" health state was further subdivided into the four NYHA classes to model disease progression.[1] A patient's NYHA class could improve or worsen over the modelled cycles.[1] A proportion of patients in NYHA classes II to IV could receive a heart transplant and transition to the "alive with transplant" health state, represented by a set of tunnel states in which patients first enter a one-month post-transplant state and then proceed into a "greater than or equal to two months post-transplant" state in subsequent model cycles.[1] Once in the "alive with transplant" health state, patients could not transition back to the "alive without transplant" health state.[1]

Baseline patient characteristics were based on the ATTR-ACT trial (89% male, 75 years of age).[1] The CUA consisted of two subgroups: patients with a baseline NYHA class I/II and NYHA class III, which the model runs separately. Model results were then weighted based on the proportion of patients in each subgroup, which was derived from the distribution of patients in ATTR-ACT with baseline NYHA class I/II (66.54%) and NYHA class III (33.46%).[2] The Markov model uses one-month cycle lengths and follows a cohort of 1,000 patients over a lifetime time horizon (30 years).[1]

Figure 1: Sponsor's Model Structure



NYHA = New York Heart Association.

Source: Sponsor's pharmacoeconomic submission.[2]

Table 10: Data Sources

Data Input	Description of Data Source	Comment
Baseline characteristics	Mean age, proportion of males, and NYHA class taken as the average of the tafamidis meglumine 80 mg and BSC groups of the ATTR-ACT trial.[2]	Appropriate. The clinical experts consulted for this review reported that ATTR-CM predominantly affects males and older individuals. They also reported that the distribution of patients initiating tafamidis meglumine is similar to the model's baseline distribution.
Efficacy	**Trial period (months 0 to 30):** The probability of being in an NYHA class was informed by the longitudinal data for the total ITT population from the ATTR-ACT trial using a last observation carried forward assumption for missing data.[2] The ATTR-ACT trial collected data at six-month assessment points; therefore, six-month distributions were applied for six-month probabilities and transitions were possible only at the end of each six-month period.[1]	Incorporating the treatment effects from the trial into the model was considered inappropriate. See "Limitations of the Sponsor's Submission" within the main report.
	Extrapolation period (beyond month 30): A two-step process was taken: 1. The probability of death by NYHA class was used to remove patients who died during each cycle from their respective NYHA classes. 2. Transition probabilities between NYHA classes for those who remained alive were estimated using the ATTR-ACT trial transitions observed between months 18 to 30.[2]	If more patients were expected to die in the NYHA class than the number of patients remaining in that class, additional patients were removed from the NYHA class that had the most patients in it. This did not occur in the tafamidis meglumine trace; however, patients in the BSC trace did get redistributed. The effect of this on the model results is unknown. The long-term efficacy data are highly uncertain. See "Limitations of Sponsor's Submission" within the main report. Additionally, it was unclear whether long-term efficacy transitions were informed by tafamidis meglumine 80 mg or by the pooled tafamidis meglumine data from the ATTR-ACT trial.
	Discontinuation: Treatment discontinuation was based on the proportion of patients in the ATTR-ACT trial who remained on tafamidis meglumine 80 mg, excluding those who discontinued due to death, transplant, or cardiac device implantation. An exponential function was fitted to the trial-reported discontinuation data and was applied to the entire model's time horizon.	Inappropriate. See "Limitations of Sponsor's Submission" within the main report. The exponential curve had the lowest AIC and BIC of the seven statistical distributions tested.[1] Discontinuation was assumed not to differ by NYHA class.[1] Clinical experts consulted for this review noted this is appropriate, as a patient's willingness to remain on treatment is not expected to depend on their current or baseline NYHA class.
	Hospitalization: All "alive without transplant" patients were at risk of cardiovascular-related hospitalization. Rates of hospitalization were treatment-specific and stratified by subgroup according to baseline NYHA class. Rates were derived from the ATTR-ACT trial and converted to a per-cycle probability of hospitalization.[2]	Inappropriate. See "Limitations of Sponsor's Submission" within the main report.

Data Input	Description of Data Source	Comment
	Transplantation: The probability of receiving a transplant is dependent on NYHA class and treatment group, according to rates observed in the ATTR-ACT trial.[2]	The clinical panel conducted by CADTH indicated that heart transplants or combined heart-liver transplants would be considered for a highly selective group of patients with advanced heart failure, but not for those whose condition was so severe that it would contradict a transplant. In the model, tafamidis meglumine patients in NYHA class IV had a 1.33% per-cycle probability of transplant, whereas it was 0% for BSC patients.[1] This may not be reflective of clinical practice, as the probability of transplant may not differ by treatment assignment. Given structural uncertainties as to the role of transplant, a scenario analysis was conducted whereby the probability of patients receiving a transplant was set to zero for tafamidis meglumine and BSC, thereby removing transplant from the model.
Natural history	For those without a heart transplant, the natural history of ATTR-CM is captured through progression through NYHA classes, based on the BSC treatment group (transition probabilities informed by the ATTR-ACT trial).[2] For those with a transplant, natural history was captured within the "greater than or equal to two months post-transplant" health state.[1]	The clinical expert consulted for this review reports that NYHA class is an appropriate but unvalidated means of measuring disease progression in ATTR-CM patients.
Utilities	A post-hoc analysis of ATTR-ACT trial data was performed to calculate EQ-5D-3L utility weights based on Canadian value sets by treatment arm. No disutilities due to AEs or hospitalizations were included, as these were assumed to be captured in the trial-based EQ-5D data. Health state utilities for patients in "alive with transplant" states were sourced from Long et al. (2014).[15]	Inappropriate. Utility values should be specific to the health state and independent of treatment. See "Limitations of Sponsor's Submission" within the main report. Inappropriate. This approach is not transparent, as the magnitude at which hospitalization or AEs may result in utility decrements is unclear. As these were not modelled explicitly, this could have led to a random probabilistic draw with higher AEs/hospitalization rates and also improved utility values. Uncertain, but unlikely to impact the model. Given a paucity of data regarding heart transplant utilities for ATTR-CM patients, it may be appropriate to use utilities for transplants in a different patient population. The 0.76 utility value was estimated from a UK study; therefore, it may be less generalizable to Canada.[4]
AEs (Indicate which specific AEs were considered in the model)	AEs of clinical importance (tier 1 events) were considered in the model. These included diarrhea and urinary tract infections.[1]	Uncertain, but unlikely to influence model results. The two tier 1 AEs considered in the model occurred with greater frequency in the BSC group than in the tafamidis meglumine group.

Data Input	Description of Data Source	Comment
Mortality	Mortality due to non–transplant related causes was informed by the all-cause overall survival data from the ATTR-ACT trial, censored for transplants and cardiac device implantations.[2] All-cause survival curves were estimated based on subgroup (i.e., overall survival for baseline NYHA class I/II and baseline NYHA class III) and treatment arm.[2] Seven parametric models were fitted to the survival data with the following distributions selected by first ruling out clinically implausible outcomes and then selecting based on statistical fit: • tafamidis meglumine, NYHA class I/II and class III: gamma distribution • BSC, NYHA class I/II and class III: Gompertz distribution.	Inappropriate. See Limitations of Sponsor's Submission within the main report.
	Patients receiving transplant had a 7.7% and 0.6% probability of experiencing peri-operative and post-transplant death (≥ 2 months), respectively.[3] These estimates were calculated by the sponsor based on data from the registry of the International Society for Heart and Lung Transplantation from 1982 to 2013.[3]	This international registry included patients who received transplants since 1982 and it is unclear whether survival from this time period and from different settings would be relevant to Canadian patients with ATTR-CM receiving heart transplants today. Data from this registry also includes pediatric patients, and it is unclear if the pediatric data were used to inform the model's mortality estimates.[3] However, this is unlikely to be a key driver of the model.
Resource use and costs		
Drug	Price of tafamidis meglumine submitted by the sponsor.[1]	Appropriate.
	RDI for tafamidis meglumine derived from mean adherence of ITT patients in the 80 mg tafamidis meglumine arm: 97.8% (from the ATTR-ACT trial).[2]	Inappropriate. See "Limitations of Sponsor's Submission" within the main report.
	Cost of BSC, including diuretics, blood pressure management, blood thinners, and anti-rhythmic medications were not included in the model.	Not including these drug costs may be conservative if treatment with tafamidis meglumine reduces the number of supportive medications required by patients. These costs are likely to be small and are unlikely to influence model results.
Event	Hospitalization: Cost per day of cardiovascular-related hospitalization is $1,190.09. Source: OCCI.[8]	Unable to validate cost for cardiovascular-related hospitalization or transplant on OCCI; however, this is unlikely to influence model results.
	Transplant: Transplant and 30-day post-transplant cost is $168,091.41. Source: OCCI.[8]	
	Duration of hospitalization was based on treatment arm and baseline NYHA, based on ATTR-CM trial.[2]	Inappropriate. According to the clinical experts consulted by CADTH for this review, a patient's duration of hospitalization is not expected to differ by treatment. See "Limitations of Sponsor's Submission" within the main report.

Data Input	Description of Data Source	Comment
	End-of-life costs: $1,472.70.[9]	Unable to validate end-of-life costs from source, but unlikely to influence model results.
AEs	Monthly AE costs for diarrhea and urinary tract infection from OCCI.[8]	Unable to validate costs on OCCI. Unlikely to influence model results.
Health state	Background resource costs were considered by NYHA class and included cardiologist, gastroenterologist, neurologist, general practitioner, and ER visits. Costs do not differ by treatment arm.	According to the clinical expert consulted by CADTH for this review, approximately half of NYHA class III and class IV patients will visit a nephrologist every three months, in addition to other specialists.
	Frequency of visits, by NYHA class, estimated from a survey of two ATTR-CM specialists in Canada.	According to the clinical expert consulted by CADTH for this review, the frequency of a patient's visits to gastroenterologists and neurologists is not expected to differ by NYHA class. Additionally, they noted that patients in NYHA class III and class IV are seen by nurse practitioners approximately every month in a cardiovascular clinic.
	Unit costs of visits sourced from the Ontario Schedule of Benefits and the OCCI.[8,16]	Appropriate costing sources.
	Post-transplant month 2+ costs: $2,965.52. Includes costs of immunosuppressants and pharmacy costs.[17]	Unable to validate post-transplant costs from source. Unlikely to influence the model results.

AE = adverse events; AIC = Akaike's information criterion; ATTR-CM = transthyretin-mediated amyloidosis cardiomyopathy; BIC = Bayesian information criterion; BSC = best supportive care; EQ-5D = EuroQol 5-Dimensions; EQ-5D-3L = EuroQol 5-Dimensions 3-Levels; ER = emergency room; ITT = intention to treat; NYHA = New York Heart Association; OCCI = Ontario Case Costing Initiative; OSB = Ontario Schedule of Benefits; RDI = relative dose intensity.

Table 11: Sponsor's Key Assumptions

Assumption	Comment
Patients in the "alive without transplant" health states who do not discontinue treatment receive tafamidis meglumine for the entire model time horizon.	Appropriate. According to the clinical experts consulted by CADTH for this review, clinicians would be unlikely to initiate tafamidis meglumine for patients in NYHA class IV. However, clinicians would be unlikely to discontinue treatment for patients in earlier NYHA classes who initiate tafamidis meglumine and later transition to NYHA class IV.
Patients may only receive a transplant once.	Appropriate.
After receiving a transplant, patients may only progress to death (i.e., no further cardiac disease progression is assumed to occur).	Uncertain, but unlikely to influence model results. According to the clinical panel conducted by CADTH, TTR deposition may still occur after transplant; however, it is unclear whether these patients would require additional treatment.
Patients who receive a transplant are no longer eligible to receive tafamidis meglumine.	Uncertain. Patients who entered the ATTR-ACT trial had not received prior transplants, so the role of tafamidis meglumine in transplant patients is unknown. According to the clinical panel conducted by CADTH, the role of tafamidis meglumine in patients who have received tafamidis meglumine is unknown.
A patient's health-related quality of life immediately after transplant remains the same for their entire lifetime.	Inappropriate. Patients would be expected to have worse health-related quality of life in the first month following transplant compared with subsequent months. This finding is supported by Pinson et al. (2000), who found that a patient's quality of life, as measured by Karnofsky scores, was lowest immediately post-transplant and improved in subsequent months.[18] However, given the small percentage of patients receiving transplants in the model, this is unlikely to influence model results.

NYHA = New York Heart Association; TTR = transthyretin.

Sponsor's Results

Table 12: Results of Sponsor's Sensitivity Analyses

Scenario	Incremental costs ($)	Incremental QALYs	Incremental cost per QALY ($)
Sponsor's base case	790,379	3.20	247,069
15-year time horizon	749,354	2.49	301,540
Survival extrapolated with Gompertz distribution for BSC and exponential for tafamidis meglumine	881,589	3.98	221,392
Survival extrapolated with gamma distribution for BSC and tafamidis meglumine	770,341	2.30	335,608
No further treatment discontinuation after month 30	1,038,604	3.20	324,663

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

Source: Sponsor's pharmacoeconomic submission.[1]

CADTH Reanalyses

Table 13: Sponsor's Frequency Estimates for Background Resource Use

		Annual frequency per patient			
Resource	Unit cost ($)	NYHA class I	NYHA class II	NYHA class III	NYHA class IV
ATTR-CM specialist visit (cardiologist)	300.70	1	2	3	4
Other specialist visit (gastroenterologist, neurologist)	333.35	1	2	3	4
Primary care	77.20	1	2	3	4
Emergency room visit	578.97	0	1	2	5
Per-cycle cost	–	59.27	166.79	274.31	478.32

ATTR-CM = transthyretin-mediated amyloidosis cardiomyopathy; NYHA = New York Heart Association.

[a] Sponsor pharmacoeconomic submission.[1]

Table 14: Reanalysis Frequency Estimates for Background Resource Use

		Annual frequency per patient			
Resource	Unit cost ($)	NYHA class I	NYHA class II	NYHA class III	NYHA class IV
ATTR-CM specialist visit (cardiologist)	300.70	1	2	3	4
Nephrologist visit	157.00[a]	0	0	2	2
Other specialist visit (gastroenterologist, neurologist)	333.35	1	2	3	4
Primary care	77.20	1	2	3	12
Emergency room visit	578.97	0	1	2	5
Per-cycle cost	–	59.27	166.79	300.47	555.95

ATTR-CM = transthyretin-mediated amyloidosis cardiomyopathy; NYHA = New York Heart Association.

[a] Ontario Schedule of Benefits code A165.

Table 15: CADTH Reanalysis

	Total costs ($)	Total LYs	Total QALYs	Incremental cost ($)	Incremental LYs	Incremental QALYs	Incremental cost per LY ($)	ICUR ($/QALY)
BSC	49,510	3.34	2.37					
Tafamidis meglumine	945,005	6.01	4.39	895,494	2.66	2.02	336,056	443,694

BSC = best supportive care; ICUR = incremental cost-utility ratio; LY = life-year; QALY = quality-adjusted life-year.

Table 16: CADTH Scenario Analyses

	Scenario	Treatments	QALYs	Cost ($)	ICUR ($/QALY)
6	CADTH base-case reanalysis	BSC	2.37	49,510	443,694
		Tafamidis meglumine	4.39	945,005	
6a	All patients start in NYHA class I/II	BSC	2.83	58,598	411,053
		Tafamidis meglumine	5.55	1,175,785	
	All patients start in NYHA class III	BSC	1.48	31,693	699,242[a]
		Tafamidis meglumine	2.14	495,885	
6b	No AEs	BSC	2.37	49,203	437,524
		Tafamidis meglumine	4.44	954,640	
6c	No transplant	BSC	2.19	33,923	479,924
		Tafamidis meglumine	4.16	977,623	
6d	No difference in the probability of CV-related hospitalization between treatments	BSC	2.37	42,495	449,525
		Tafamidis meglumine	4.37	940,777	
6e	Sponsor's estimate for treatment adherence (97.8%)	BSC	2.37	49,396	431,713
		Tafamidis meglumine	4.41	929,459	

AE = adverse event; CV = cardiovascular; ICUR = incremental cost-utility ratio; NYHA = New York Heart Association; QALY = quality-adjusted life-year.

[a] Results were highly unstable due to uncertainty in the Gompertz distribution. When the parameters defining the Gompertz survival curves were assumed to be fixed values, the ICUR in this scenario increased to $818,390 per QALY.

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