

## CADTH COMMON DRUG REVIEW

# CADTH Canadian Drug Expert Committee Recommendation

(Final)

### TAFAMIDIS MEGLUMINE (VYNDAQEL – PFIZER CANADA ULC)

Indication: For the treatment of adult patients with cardiomyopathy due to transthyretin-mediated amyloidosis, wild-type or hereditary.

#### RECOMMENDATION

The CADTH Canadian Drug Expert Committee recommends that tafamidis be reimbursed for the treatment of adult patients with cardiomyopathy due to transthyretin (TTR)-mediated amyloidosis, wild-type or hereditary, to reduce cardiovascular mortality and cardiovascular-related hospitalization only if the following conditions are met.

#### Conditions for Reimbursement

##### Initiation Criteria

1. Documented cardiac disease due to TTR-mediated amyloidosis cardiomyopathy (ATTR-CM).
  - 1.1. Documented wild-type ATTR-CM consists of all of the following: absence of a variant TTR genotype; evidence of cardiac involvement by echocardiography with end diastolic interventricular septal wall thickness of greater than 12 mm; presence of amyloid deposits in biopsy tissue (fat aspirate, salivary gland, median nerve connection tissue sheath, or cardiac); and TTR precursor protein identification by immunohistochemistry, scintigraphy, or mass spectrometry.
  - 1.2. Documented hereditary ATTR-CM consists of all of the following: presence of a variant TTR genotype associated with cardiomyopathy and presenting with a cardiomyopathy phenotype; evidence of cardiac involvement by echocardiography with end diastolic interventricular septal wall thickness of greater than 12 mm; presence of amyloid deposits in biopsy tissue (fat aspirate, salivary gland, median nerve connective tissue sheath, or cardiac).
2. Patients who have all of the following characteristics:
  - 2.1. New York Heart Association (NYHA) class I to III
  - 2.2. history of heart failure, defined as at least one prior hospitalization for heart failure or clinical evidence of heart failure that required treatment with a diuretic
  - 2.3. have not received a heart or liver transplant
  - 2.4. do not have an implanted cardiac mechanical assist device (CMAD)
  - 2.5. not receiving other disease-modifying treatments for ATTR.

##### Discontinuation Criteria

1. Treatment with tafamidis should be discontinued for patients who:
  - 1.1. progress to NYHA class IV, or
  - 1.2. receive a heart or liver transplant, or
  - 1.3. receive an implanted CMAD.

##### Prescribing Conditions

1. The patient must be under the care of a specialist with experience in the diagnosis and management of ATTR-CM.

##### Pricing Conditions

1. Price reduction.

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## TAFAMIDIS MEGLUMINE (VYNDAQEL – PFIZER CANADA ULC)

Indication: For the treatment of adult patients with cardiomyopathy due to transthyretin-mediated amyloidosis, wild-type or hereditary.

### Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that tafamidis be reimbursed for the treatment of adult patients with cardiomyopathy due to transthyretin (TTR)-mediated amyloidosis, wild-type or hereditary, to reduce cardiovascular mortality and cardiovascular-related hospitalization only if the following conditions are met.

### Conditions for Reimbursement

#### Initiation Criteria

1. Documented cardiac disease due to TTR-mediated amyloidosis cardiomyopathy (ATTR-CM)
  - 1.1. Documented wild-type ATTR-CM consists of all of the following: absence of a variant TTR genotype; evidence of cardiac involvement by echocardiography with end diastolic interventricular septal wall thickness of greater than 12 mm; presence of amyloid deposits in biopsy tissue (fat aspirate, salivary gland, median nerve connection tissue sheath, or cardiac); and TTR precursor protein identification by immunohistochemistry, scintigraphy, or mass spectrometry.
  - 1.2. Documented hereditary ATTR-CM consists of all of the following: presence of a variant TTR genotype associated with cardiomyopathy and presenting with a cardiomyopathy phenotype; evidence of cardiac involvement by echocardiography with end diastolic interventricular septal wall thickness of greater than 12 mm; presence of amyloid deposits in biopsy tissue (fat aspirate, salivary gland, median nerve connective tissue sheath, or cardiac)
2. Patients who have all of the following characteristics:
  - 2.1. New York Heart Association (NYHA) class I to III
  - 2.2. history of heart failure, defined as at least one prior hospitalization for heart failure or clinical evidence of heart failure that required treatment with a diuretic
  - 2.3. have not received a heart or liver transplant
  - 2.4. do not have an implanted cardiac mechanical assist device (CMAD)
  - 2.5. not receiving other disease-modifying treatments for ATTR.

#### Discontinuation Criteria

1. Treatment with tafamidis should be discontinued for patients who:
  - 1.1. progress to NYHA class IV, or
  - 1.2. receive a heart or liver transplant, or
  - 1.3. receive an implanted CMAD.

#### Prescribing Conditions

1. The patient must be under the care of a specialist with experience in the diagnosis and management of ATTR-CM.

#### Pricing Conditions

1. Price reduction.

### Reasons for the Recommendation

1. In one double-blind, phase III, randomized controlled trial in patients with wild-type or hereditary ATTR-CM, treatment with tafamidis 80 mg was associated with reduced mortality and cardiovascular-related hospitalizations after 30 months compared with placebo. At month 30, more patients were alive in the tafamidis 80 mg group compared with the placebo group (69.3% versus 57.1%). There were also more cardiovascular-related hospitalizations in the placebo group compared with tafamidis 80 mg, among patients who were alive at month 30 (mean: 0.46 per year versus 0.34 per year). Clinically important differences were also observed in favour of tafamidis at month 30 in health-related quality of life, as measured by the Kansas City Cardiomyopathy Questionnaire (KCCQ) overall score (least square mean difference for tafamidis 80 mg versus placebo: 13.5 points; 95% confidence interval [CI], 9.2 to 17.8), and disability progression, as measured by the 6-minute walk test (6MWT) (least square mean change of -54.8 metres versus -130.6 metres).

2. There is an unmet clinical need due to the absence of effective alternative treatments for ATTR-CM. There are no other approved treatment options that address the underlying mechanism of the disease and are supported by robust evidence.
3. Patients classified as NYHA class IV (i.e., unable to carry on any physical activity without discomfort, symptoms of heart failure at rest, if any physical activity is undertaken discomfort increases) at baseline and those who had prior liver or heart transplant or an implanted CMAD were excluded from the study. If, during the study, a patient chose to accept a donor organ transplant or had implantation of a CMAD, the patient was discontinued from the study. Therefore, there is no evidence to support the use of tafamidis in these patients.
4. The sponsor-submitted price of tafamidis is \$133.57 per 20 mg capsule. At a dose of tafamidis 80 mg daily, the cost of tafamidis is \$534 daily and \$195,012 annually. Based on a CADTH reanalysis of the sponsor-submitted economic model, the incremental cost-utility ratio (ICUR) for tafamidis compared with best supportive care (BSC) is \$443,694 per quality-adjusted life-year (QALY) gained. However, this estimate is associated with significant uncertainty due to limitations in the submitted model structure. Based on the CADTH reanalysis, a price reduction of more than 92% is required for tafamidis to achieve an ICUR of \$50,000 per QALY.

## Implementation Considerations

- Diagnosis of hereditary or wild-type ATTR-CM requires specialized testing for amyloid protein, scintigraphy, or genetic testing, which are available at larger academic centres.
- The classification of patients according to NYHA class depends on clinician judgment; there are no laboratory or imaging criteria that designate a patient as having transitioned from NYHA class III to NYHA class IV. This judgment will rely on clinical assessments only.
- The prevalence of wild-type ATTR-CM is unknown and some evidence indicates that wild-type ATTR may be underdiagnosed. The budget impact of tafamidis may be considerable given the high cost of the drug. Even at a substantially reduced price, CDEC discussed that the budget impact of tafamidis could be even greater if the prevalence of wild-type ATTR is higher than currently recognized. The availability of an effective treatment may also stimulate diagnostic testing with further impact on health system resources. CDEC also discussed that the diagnostic accuracy of currently used tests among the broad spectrum of patients with restrictive cardiomyopathy is unknown.

## Discussion Points

- CDEC acknowledged that many patients receiving tafamidis will likely experience some worsening of their symptoms over time, but that these patients may nevertheless continue to benefit from treatment with tafamidis as their disease trajectory may have been more rapid had they not received the drug.
- There is no evidence to support the use of tafamidis in combination with other TTR stabilizers or interfering ribonucleic acid drugs that may be used to treat other symptoms of ATTR, such as polyneuropathy.
- Patients who are asymptomatic with cardiac involvement who do not have a history or clinical evidence of heart failure were not included in the ATTR-ACT trial. The benefit of treatment with tafamidis in this patient population is unknown.
- CDEC discussed that while analyses of the tafamidis 80 mg dose were exploratory in the ATTR-ACT study, results were aligned with the primary analysis conducted in the pooled tafamidis 80 mg and 20 mg group. Further, two-thirds of patients in the pooled dose group received 80 mg tafamidis.

## Background

Tafamidis meglumine is a selective TTR stabilizer that binds to thyroxine binding sites, thus stabilizing the TTR tetramer. The Health Canada indication for tafamidis is for the treatment of adult patients with cardiomyopathy due to TTR-mediated amyloidosis, wild-type or hereditary, to reduce cardiovascular mortality and cardiovascular-related hospitalization. Tafamidis is available as a 20 mg capsule. The recommended dose of tafamidis meglumine is 80 mg (administered as four 20 mg capsules) taken orally, once daily, with or without food. The dose may be reduced to 20 mg if not tolerated.

## Summary of Evidence Considered by CDEC

The committee considered the following information prepared by CADTH: a systematic review of randomized controlled trials of tafamidis and a critique of the manufacturer's pharmacoeconomic evaluation. The committee also considered input from clinical experts with experience in treating patients with ATTR-CM, and patient group–submitted information about outcomes and issues important to patients.

### Summary of Patient Input

The Canadian Organization for Rare Disorders, with support from the Canadian Amyloidosis Support Network, provided input for this review. Patient perspectives were obtained from an online survey and individual patient interviews. The following is a summary of key input from the perspective of the patient group:

- Almost all patients (or caregivers) reported that the condition was debilitating, interfering significantly with daily functioning and quality of life. Like all types of ATTR, the condition affects multiple systems in the body.
- The patient group indicated that prior to tafamidis, there have been no therapies specific for ATTR-CM. Almost all patients (86%) reported receiving treatments to manage symptoms related to organ damage, namely heart damage, nerve damage, and inflammation. The therapies reported as used by most respondents (67%) included medicines to manage fluid and/or mineral levels (e.g., electrolytes, and mineral and vitamin supplements). About half (50% to 54%) were currently taking some form of cardiac management therapy to manage blood pressure (e.g., diuretics), regulate heartbeat (e.g., amiodarone), or minimize clots (e.g., warfarin). Diflunisal, a nonsteroidal anti-inflammatory drug, was being used by about one-third of patients, with one-third reporting previous diflunisal use. Only two respondents indicated receipt of a liver transplant; one of them resided in Canada and the other in the US. Respondents indicated that the current treatments, including liver transplant, were “not at all” or “somewhat” effective in managing symptoms.
- The responses reflected both optimism and realism. The patient group reported two types of benefits. The first referenced the impact on symptoms, namely reduction in nerve pain, increase in strength and energy, better appetite, and improved mobility. The second benefit was “slowing or halting” disease progression. Thus, in their day-to-day life, patients felt better and were able to do more. As important, they were optimistic that this insidious disease was being held in check, if not actually cured.

### Clinical Trials

The systematic review included one phase III clinical trial (ATTR-ACT). The ATTR-ACT study was a multi-centre, double-blind, randomized, placebo-controlled trial in adults with hereditary or wild-type ATTR-CM. A total of 441 patients were randomized in a 2:1:2 ratio to placebo (N = 177), tafamidis 20 mg (N = 88), or tafamidis 80 mg (N = 176) once daily for 30 months. Randomization was stratified by wild-type or hereditary ATTR-CM, and NYHA class I or class II/III. In the primary analysis, patients receiving the 20 mg and 80 mg of tafamidis were pooled, whereas exploratory analyses by dose group were conducted for the primary and key secondary outcomes. In the Health Canada product monograph for tafamidis, the dosage indicated for ATTR-CM is 80 mg once daily, administered as four 20 mg capsules. Therefore, the focus of the CADTH review was the tafamidis 80 mg treatment group.

The study was completed by 48% of patients in the placebo group and 64.2% in the tafamidis 80 mg group. More patients in the placebo group discontinued treatment (52% placebo versus 35.8% tafamidis 80 mg). The main reason for discontinuation was death, which was higher in the placebo group than in the tafamidis 80 mg group (21.5% versus 14.2%). Other common reasons were withdrawal of consent (20.9% versus 9.7%) and adverse events (AEs) (6.2% versus 6.8%) in the placebo and tafamidis 80 mg groups, respectively.

### Outcomes

Outcomes were defined a priori in the CADTH systematic review protocol. Of these, the committee discussed the following:

- Combination of all-cause mortality and frequency of cardiovascular-related hospitalization at month 30: Analyzed with a hierarchical statistical testing approach and applying the method of Finkelstein-Schoenfeld. In this method, each patient was compared with every other patient within strata (i.e., wild type or hereditary and NYHA class I/II combined or class III) in a pairwise fashion, on all-cause mortality first, followed by cardiovascular-related hospitalization if patients could not be ranked based on mortality. All rankings were then combined to produce an overall test statistic.

- The KCCQ overall score: A 23-item (15-question) disease-specific health-related quality of life questionnaire used for patients with congestive heart failure. The KCCQ consists of eight domains (physical limitation, symptom stability, symptom frequency, symptom burden, total symptoms, self-efficacy, quality of life, and social limitation), a clinical summary, and an overall summary score. The scores are transformed to a 0 to 100 range, with higher scores indicating better health status. The KCCQ has been considered as a reliable and valid self-report instrument for measuring disease-specific quality of life in chronic heart failure. The KCCQ has been validated in patients with congestive heart failure with a minimal important difference (MID) of 5.7 for the overall score. However, no data were available for the validity or MID of the KCCQ in patients with ATTR-CM.
- NYHA functional classification: A measurement designed to assess the severity of heart failure that consists of four categories (class I, class II, class III, and class IV).
- 6MWT: A supervised test that measures the distance a patient can walk on a hard, flat surface over a six-minute period. The 6MWT is a commonly used test to evaluate global function of organ systems involved in exercise, namely the heart, lungs, peripheral circulation, blood, nervous system, muscles, bones, and joints during walking, a self-paced activity. No MIDs were identified for patients with ATTR-CM.
- N-terminal prohormone of brain natriuretic peptide (NT-proBNP): A cardiac biomarker that is released from the heart into blood circulation in response to myocardial wall tension and stress. NT-proBNP has been validated as a marker of cardiac stress and injury in patients with TTR amyloidosis (hereditary and wild type). It is a valid surrogate marker for mortality in patients with hereditary ATTR.
- Echocardiograms: A measure of cardiac left ventricle (LV) systolic function. Echocardiogram parameters (e.g., LV longitudinal strain, LV end diastolic interventricular septal wall thickness [mm]; LV wall thickness, and LV ejection fraction) are a reliable examination commonly used in clinics.
- Harms.

The primary outcome was a hierarchical combination of all-cause mortality and cardiovascular-related hospitalization at month 30 analyzed by the Finkelstein-Schoenfeld method.

### Efficacy

- For the primary outcome, at month 30, more patients were alive in the tafamidis 80 mg group compared with placebo (69.3% versus 57.1%). There were also more cardiovascular-related hospitalizations in the placebo group compared with tafamidis 80 mg among patients who were alive at month 30 (mean: 0.46 per year versus 0.34 per year). In the primary analysis that compared the pooled tafamidis dose group with placebo, the results demonstrated a pattern that was similar to tafamidis 80 mg. The Finkelstein-Schoenfeld analysis was statistically significant for the pooled tafamidis group versus placebo ( $P = 0.0006$ ), demonstrating that at least one, or possibly both, of all-cause mortality and cardiovascular-related hospitalization were statistically significantly different.
- Health-related quality of life was measured using the KCCQ and was a key secondary outcome in the ATTR-ACT study. For the KCCQ overall score, the change from baseline to month 30 was  $-7.3$  points in the tafamidis 80 mg group,  $-7.2$  points for the pooled tafamidis group, and  $-20.8$  points for the placebo group, indicating a relatively more rapid decline in patients' health-related quality of life as measured by KCCQ over the 30-month period for the placebo group. The least square mean difference for tafamidis 80 mg versus placebo was 13.5 points (95% CI, 9.2 to 17.8), and 13.7 points (95% CI, 9.5 to 17.8) for the pooled tafamidis group versus placebo. These estimates exceed the MID of 5.7 for patients with congestive heart failure.



- Disability was measured using the 6MWT and was a key secondary outcome in ATTR-ACT. The decrease in the 6MWT from baseline to month 30 was smaller for tafamidis 80 mg compared with placebo (least square mean change:  $-54.8$  metres versus  $-130.6$  metres). Similarly, the decrease was smaller for the pooled tafamidis group compared with placebo ( $-54.9$  metres). The least square mean difference for the pooled tafamidis group versus placebo was 75.7 metres (95% CI, 57.6 to 93.8). Although no MID for the 6MWT test is available specifically for patients with ATTR-CM, these estimates exceeded the MID of 43 metres for heart failure.

- The NT-proBNP cardiac biomarker was an exploratory outcome. The NT-proBNP level in both the pooled tafamidis group and the placebo group increased from baseline to month 30; however, the increase was smaller for the pooled tafamidis group compared with the placebo group (least square mean change from baseline 1,771.7 pg/mL versus 3,947.7 pg/mL).
- Changes from baseline to month 30 in echocardiogram parameters were exploratory in ATTR-ACT. Smaller magnitudes of changes were observed for global longitudinal strain, LV end diastolic interventricular septal wall thickness, LV posterior wall thickness, and left ventricular ejection fraction for the pooled tafamidis group compared with the placebo group.

## Harms (Safety)

- AE: Almost all patients experienced at least one AE (98.9% placebo, and 98.3% tafamidis 80 mg). The most common AEs were cardiac-related (atrial fibrillation: 18.6% placebo, 19.9% tafamidis 80 mg); cardiac failure (33.9% placebo, 26.1% tafamidis 80 mg). Gastrointestinal effects, such as constipation (16.9% placebo, 14.8% tafamidis 80 mg), diarrhea (22.0% placebo, 12.5% tafamidis 80 mg), and nausea (20.3% placebo, 11.4% tafamidis 80 mg) were also common, but experienced by a lower percentage of patients who received tafamidis rather than placebo.
- Serious adverse events (SAE): At least one SAE was experienced by 79.1% of patients in the placebo group and 75.6% of patients in tafamidis 80 mg group. The most common SAEs were cardiac-related (i.e., atrial fibrillation and cardiac failure) and condition aggravated (32.8% placebo, 22.7% tafamidis 80 mg).
- Withdrawals due to AE: More patients in the placebo group stopped treatment due to an AE (29% placebo, 23% tafamidis 80 mg); however, withdrawal from the study due to an AE was similar between the placebo group (6.2%) and the tafamidis 80 mg (6.8%) group.
- Notable harms: Hypothyroidism was experienced by 5.6% of patients in the placebo group and 6.8% of patients in the tafamidis 80 mg group. More patients who received tafamidis had thyroxine abnormality of less than 0.8 lower limit of normal (4.5% placebo, 29.9% tafamidis 80 mg). Pruritis or rash occurred in more patients in the placebo group.

## Indirect Treatment Comparisons

No indirect evidence was submitted by the sponsor. An independent literature search for indirect evidence conducted by CADTH did not identify any evidence that met the inclusion criteria of the CADTH review protocol.

## Cost and Cost-Effectiveness

Tafamidis is available as a 20 mg capsule at a submitted price of \$133.57 per capsule. At the recommended dose of 80 mg, the daily and annual drug costs for tafamidis are \$534 and \$195,012 per patient, respectively.

The sponsor submitted a cost-utility analysis from the perspective of a Canadian publicly funded health care payer comparing tafamidis with BSC (consisting of supportive care medications) in patients with ATTR-CM over a lifetime time horizon (30 years). A multi-state cohort Markov model was developed, with three main health states: alive without transplant, alive with transplant, and death. Within the alive without transplant health state, patients were further subdivided into the four NYHA classes to reflect cardiac disease progression and, 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). Patients entered the model distributed across one of two subgroups (baseline NYHA I/II or NYHA III) The model considered the two subgroups separately with the results weighted by the baseline NYHA class distributions (i.e., 67% in NYHA I/II and 33% in NYHA III) to produce the cost-effectiveness estimates for the full population. Transition probabilities on cardiac disease progression and transplantation were derived from the ATTR-ACT trial. Treatment-specific utilities and treatment and baseline NYHA-dependent mortality for patients in the alive without transplant health states were estimated from the ATTR-ACT trial. The model assumed that patients in the alive without transplant health states would remain on treatment, irrespective of NYHA class. Treatment acquisition costs were adjusted by the compliance rate and the extrapolated treatment discontinuation observed in the ATTR-ACT trial over the entire model time horizon. No treatment costs were assumed to be associated with BSC. Other costs included the costs of physician visits, emergency room visits, and cardiovascular-related hospitalizations.

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

- Disease progression, in terms of mortality and cardiovascular-related hospitalization, was 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.
- Treatment discontinuation and efficacy were modelled independently, resulting in ongoing reductions in treatment acquisition costs 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.
- Despite using one-month cycle lengths, during the first 30 months of the model, changes in cardiac disease progression occurred every six months, which would not be realistic in clinical practice.
- Treatment-specific health-state utility values were used.
- Resource use estimates may not reflect expected Canadian treatment practices.
- Tafamidis treatment costs were reduced by assuming lowered rates of adherence.
- There was uncertainty regarding the long-term clinical efficacy of tafamidis and the initiation of tafamidis in NYHA class IV due to a paucity of clinical data.

CADTH's reanalyses accounted for some of the identified limitations: different distributions for survival curves were selected, treatment discontinuation was assumed to be capped at 30 months, treatment-specific health-state utilities were removed, resources used estimates were revised based on current clinical practice, and 100% adherence was assumed. This resulted in a revised ICUR for tafamidis of \$443,694 per QALY gained compared with BSC. To be considered cost-effective at a willingness-to-pay threshold of \$50,000 per QALY, a 92% reduction in price would be required.

CADTH was unable to address several structural limitations related to the economic model and uncertainty remains regarding the clinical efficacy of tafamidis beyond 30 months. The potential cost-effectiveness of tafamidis in patients with baseline NYHA class IV is unknown and was not addressed in either the sponsor's or CADTH's analyses.

## CDEC Members

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

## November 20, 2019 Meeting

### Regrets

None

### Conflicts of Interest

None