

CADTH Reimbursement Recommendation

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

Sponsor: Pfizer Canada ULC

Final recommendation: Reimburse with conditions

This recommendation supersedes the CADTH Canadian Drug Expert Committee recommendation for this drug and indication dated February 21, 2020.

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What Is the CADTH Recommendation for Vyndaqel?

CADTH recommends that Vyndaqel should be reimbursed by public drug plans for the treatment of transthyretin-mediated amyloidosis (ATTR) if certain conditions are met.

Which Patients Are Eligible for Coverage?

Vyndaqel should only be covered to treat adult patients who have a documented diagnosis of cardiomyopathy caused by ATTR. The type of ATTR cardiomyopathy could be either hereditary (inherited) or wild type (patients without a family history of the disease). Patients who are eligible for Vyndaqel coverage must also have a New York Heart Association (NYHA) classification of I to III and a history of heart failure. Patients who have received a heart transplant or a cardiac mechanical assist device (CMAD) or who are taking other disease-modifying treatments for ATTR are not eligible for reimbursement of Vyndaqel.

What Are the Conditions for Reimbursement?

Vyndaqel should only be reimbursed for patients with ATTR if they are being cared for by a specialist for the condition and if the price of Vyndaqel is reduced.

Why Did CADTH Make This Recommendation?

- Evidence from 1 clinical trial showed that patients with cardiomyopathy caused by ATTR treated with Vyndaqel were less likely to die or be hospitalized for heart-related events than patients who received placebo treatment.
- There is no evidence to support the use of Vyndaqel in patients with a NYHA classification of IV or those who have received a heart transplant or an implanted CMAD because these patients were excluded from the clinical trial.
- Based on CADTH's assessment of the health economic evidence, Vyndaqel does not represent good value to the health care system at the submitted price and requires at least a 92% price reduction

Additional Information

What Is ATTR and Cardiomyopathy?

ATTR is the excessive buildup of proteins in the body's organs. When this buildup occurs in the heart, it can cause cardiomyopathy. Cardiomyopathy caused by ATTR puts patients at risk of heart failure and death. The prevalence of cardiomyopathy caused by ATTR in Canada is unknown.

Unmet Needs in ATTR

There are no other Health Canada-approved treatment options that address cardiomyopathy caused by ATTR that are supported by robust evidence.

How Much Does Vyndaqel Cost?

Treatment with Vyndaqel is expected to cost approximately \$195,012 per patient per year.

Recommendation

This recommendation supersedes the CADTH Canadian Drug Expert Committee (CDEC) recommendation for this drug and indication dated February 21, 2020.

CDEC recommends that tafamidis be reimbursed for the treatment of adult patients with cardiomyopathy due to transthyretin (TTR)-mediated amyloidosis (ATTR), either 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; positive findings on technetium-99m pyrophosphate (Tc-99m-PYP) scintigraphy with single-photon emission computed tomography (SPECT) scanning or 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; and positive findings on Tc-99m-PYP scintigraphy with SPECT scanning or 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 1 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. are 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

- In 1 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 the tafamidis 80 mg group among those 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 m versus -130.6 m).
- 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.
- Patients classified as NYHA class IV (i.e., unable to carry on any physical activity without discomfort, symptoms of heart failure at rest, discomfort increases if any physical activity is undertaken) at baseline and those who had prior liver or heart transplant or an implanted CMAD were excluded from the study. If a patient chose to accept a donor organ transplant or had implantation of a CMAD during the study, that patient was discontinued from the study. Therefore, there is no evidence to support the use of tafamidis in these patients.
- The sponsor-submitted price of tafamidis is \$133.57 per 20 mg capsule. At a dosage 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.
- When discussing the Request for Advice, CDEC acknowledged that Tc-99m-PYP scintigraphy with SPECT scanning is now the standard practice suggested by guidelines

for diagnosis of ATTR-CM. CDEC discussed that a biopsy is indicated for diagnosing ATTR-CM only if scintigraphy is equivocal, unavailable, or discordant with clinical suspicion (i.e., ATTR is highly suspected clinically despite a negative PYP scan).

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.
- Positive findings of Tc-99m-PYP scintigraphy with SPECT scanning is defined as Perugini Grade 2 or higher uptake (greater than or equal to bone uptake), or a heart to contralateral lung uptake ratio of at least 1.5.

Discussion Points

- CDEC acknowledged that many patients receiving tafamidis will likely experience some worsening of their symptoms over time, but these patients may nevertheless continue to benefit from treatment with tafamidis because 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 dosage group received 80 mg tafamidis.
- In the CDEC meeting regarding the Request for Advice, CDEC discussed current standard practices for diagnosing ATTR and acknowledged that these have changed since the pivotal trial (ATTR-ACT) was completed. Clinical expert input, guidelines, and position statements indicated that biopsy is no longer required, and that Tc-99m-PYP scintigraphy with SPECT scanning is a non-invasive and accurate method for diagnosing ATTR-CM.

CDEC also discussed that endomyocardial biopsy is associated with a risk of serious complications that are of concern in this patient population. CDEC concluded that biopsies are only necessary in the case that results from Tc-99m-PYP scintigraphy are equivocal, unavailable, or clinical suspicion remains high despite negative results.

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 ATTR, either wild type or hereditary, to reduce cardiovascular mortality and cardiovascular-related hospitalization. Tafamidis is available as a 20 mg capsule. The recommended dosage of tafamidis meglumine is 80 mg (administered as four 20 mg capsules) taken orally, once daily, with or without food. The dosage may be reduced to 20 mg if not tolerated.

Summary of Evidence Considered by CDEC: Initial Meeting

The committee considered the following information prepared by CADTH: a systematic review of randomized controlled trials of tafamidis and a critique of the sponsor'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 before 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). Approximately half of patients (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 used by approximately one-third of patients, with one-third reporting previous diflunisal use. Only 2 respondents indicated they had received a liver transplant; 1 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 2 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 1 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 receive 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 who received the 20 mg and 80 mg dosages of tafamidis were pooled, whereas exploratory analyses by dosage 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:** These were 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 8 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 range of 0 to 100, with higher scores indicating better health status. The KCCQ is considered 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 4 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 6-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 ATTR (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, more patients were alive at month 30 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 the tafamidis 80 mg group 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 dosage group with the placebo group, the results demonstrated a pattern that was similar to the tafamidis 80 mg group. The Finkelstein-Schoenfeld analysis was statistically significant for the pooled tafamidis group versus placebo ($P = 0.0006$), demonstrating that at least 1, 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 the KCCQ over the 30-month period for the placebo group. The least square mean difference for the tafamidis 80 mg group versus the placebo group 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 the placebo group. These estimates exceed the MID of 5.7 points 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 distance from baseline to month 30 was smaller for the tafamidis 80 mg group compared with the placebo group (least square mean change: –54.8 m versus –130.6 m). Similarly, the distance decrease was smaller for the pooled tafamidis group compared with the placebo group (–54.9 m). The least square mean difference for the pooled tafamidis group versus the placebo group was 75.7 m (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 m 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 in echocardiogram parameters from baseline to month 30 were exploratory in the ATTR-ACT study. 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)

- **AEs:** Almost all patients experienced at least 1 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 than those who received placebo.
- **Serious adverse events (SAEs):** At least 1 SAE was experienced by 79.1% of patients in the placebo group and 75.6% of patients in the 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, withdrawals from the study due to an AE were 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 a thyroxine abnormality of less than 0.8, the 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 dosage 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 3 main health states: alive without transplant, alive with transplant, and death. Within the alive without transplant health state, patients were further subdivided into the 4 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 1 of 2 subgroups (baseline NYHA I/II or NYHA III) The model considered the 2 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 1-month cycle lengths, during the first 30 months of the model, changes in cardiac disease progression occurred every 6 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 that 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.

Summary of Evidence Considered by CDEC: Request for Advice

Context for the Request for Advice

In 2020, CDEC recommended that tafamidis be reimbursed for the treatment of adult patients with cardiomyopathy due to ATTR, either wild type or hereditary, to reduce cardiovascular mortality and cardiovascular-related hospitalization only if the conditions for reimbursement were met. One of the conditions for initiation in the recommendation was documented cardiac disease due to ATTR-CM. The recommendation stated that documented ATTR-CM consists of the "presence of amyloid deposits in biopsy tissue (fat aspirate, salivary gland, median nerve connective tissue sheath, or cardiac)" among other criteria. With the advent of newer diagnostic modalities that may detect the presence of amyloid deposits, the evolving role of biopsies may result in implementation challenges for jurisdictions.

The public drug plans are seeking advice on the role of biopsies and other modalities in diagnosing ATTR-CM. Specifically, the drug plans asked if biopsy is a necessary modality for diagnosing patients with cardiomyopathy due to wild-type or hereditary ATTR and for which other alternative modalities (e.g., Tc-99m-PYP scintigraphy) would be acceptable for diagnosing patients with cardiomyopathy due to wild-type or hereditary ATTR for the purposes of providing reimbursement for treatment with tafamidis (Vyndaqel).

The request for advice approach consisted of collecting stakeholder feedback from the sponsor and patient groups, consulting 2 clinical experts and conducting a literature search for relevant clinical practice guidelines. Pfizer Canada ULC and the Canadian Organization for Rare Disorders provided input to the request for advice.

Summary of Findings

The use of biopsy to confirm diagnosis is only necessary in select cases. The clinical expert panel and the 12 clinical guidelines reviewed as part of this request for advice all indicated that biopsies are only necessary in the case that results from Tc-99m-PYP scintigraphy are equivocal, clinical suspicion remains high despite negative results, or if the Tc-99m-PYP scintigraphy modality is unavailable. Clinical experts noted that the yield of non-cardiac biopsy, especially in wild-type ATTR, is highly variable and could be low, which also aligned with the findings presented in the guidelines.

Tc-99m-PYP scintigraphy is an acceptable modality for diagnosing ATTR-CM. The clinical experts and the clinical guidelines suggest that Tc-99m-PYP scintigraphy is a valid form of

non-invasive diagnosis, and that SPECT is necessary alongside PYP scanning as opposed to planar imaging alone.

Patients reported valuing diagnostic modalities that are effective and low-risk, and that they trusted their cardiologist to provide the best information and most appropriate care.

CDEC Information

Initial Meeting CDEC Members

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Meeting date: November 20, 2019

Regrets: None

Conflicts of interest: None

Request for Advice Meeting CDEC Members

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Meeting date: April 27, 2022

Regrets: None

Conflicts of interest: None